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THE SEX HORMONES IN ADVANCED BREAST CANCER*

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BALTIMORE, MARYLAND

THE treatment of cancer of the breast is one of the gravest and most formidable problems confronting the medical profession at the present time. The National Cancer Institute recently estimated that the number of new cancer cases (all sites) increased 34 per cent during the ten-year period 1937 to 1947 and that of this increase only 7 per cent was due to greater longevity. There is little comfort in the knowledge that breast cancer in the female is the most common type of cancer, according to current death rates for all malignant diseases. Statistics, compiled both in this country and abroad, reveal that 4 per cent of all women reaching the age of thirty-five are destined to die of this disease, and there is little reason to foresee any dramatic decline in this mortality rate. Cancer of the breast constitutes almost 12 per cent of all cases of cancer, regardless of sex.

Perhaps, however, it is not over-optimistic to predict that future methods of cancer therapy will probably improve. Supervoltage radiotherapy and the clinical application of isotopes will surely find an ever-increasing field of usefulness, but it is doubtful that these innovations will be spectacular or even impressive. Refinements in the technic of radical breast surgery, even when used promptly, meticulously and with the utmost of skill, can hardly become more radical. Handley's[1] allusion to the excision of the internal mammary chain of lymph nodes *in toto* after removal of all the costal cartilages has now become a surgical *fait accompli*, but it has merely added to the operative mortality without contributing greatly to the postoperative longevity. The anatomic limit of free franchise among competent breast surgeons may actually have been achieved with the ingenuity of Moore,[2] Lister[3] and Banks[4] and the simultaneous disclosures of Halsted[5] and Meyer.[6] As valuable as these triumphs of modern ultraradical surgery are, they fall far short of an absolute five-year "cure" in breast cancer. For even in the very best of surgical clinics radical mastectomy remains the preface to an ultimate autopsy (within five years) in about 50 per cent of patients. In selected and more desperate cases Wangensteen[7, 8] has been removing the contralateral breast as well as undertaking extensive thoracocervical dissection. This heroic surgery is the contemporary consummation of somatic reduction; it has yet to withstand the test of time. Its merit will rest on the ultimate survival of the patient from both the operation and the disease.

Almost two thousand years ago Celsus stated that "only the beginnings of a cancer permit of a cure." Today it is quite possible that vigorous public propaganda and professional education will expedite earlier cancer detection and more accurate cancer diagnosis. The development of a clinical laboratory test that would be "sufficiently specific to identify all cancer cases at an early stage and simple enough to be applied on a mass basis at a reasonable cost"[9] would certainly temper the time lag in the treatment of cancer.

The urgent need for an effective chemotherapeutic agent can be measured by both the merit and the limitations of present radical surgery and irradiation. Among the many difficulties of discovering a sovereign remedy for cancer is the fact that the cancer cell itself has a strong resemblance to its normal prototype. As suggested by Cade,[10] "it is this family likeness which is the key to histological study; as yet it throws no light on the cause which transforms the original normal harmless and functionally useful prototype into its coarse, nearly monstrous egocentric malignant analogue." Because of this strong family likeness, almost no known protective action is taken by the body, as would normally occur with invasive infectious agents. In the process of malignant transformation, — which appears to be both stable and almost irreversible, — cancer cells acquire the power of autonomy.

Chemical agents that are currently being used with caution in cancer therapy are for the most part potent substances that are capable of producing profound changes in both normal and abnormal tissues. Among these are a group of carcinolytic selective cell poisons, — "unfortunately more poison-

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ous than selective," — which have been shown to be able to cause some degree of tumor regression. The further development of these mitotic poisons, which have inhibitory effects on tumor growth, is of considerable interest and promise.

However, apart from specific cancer-cell toxins we are now entering a new era in cancer chemotherapy — the era of endocrines. They may prove to be the greatest *elixir vitae* of all and ultimately may find an important place in our anti-cancer armamentarium. Despite a limited basic knowledge of the sex steroids, newly discovered hormones have already proved of benefit in other almost hopeless diseases, and in cancer chemotherapy we may become even more indebted to the steroid chemists. Some of these steroid substances, which are normally present within the body, can and do control cancer growth of specific target-organ tumors. Certain patients with widespread metastases from cancer of either breast or prostate are today leading prolonged, normal and pain-free lives due to sex steroids. In the chemotherapy of cancer the hope of hormones lies in the internal alteration of the soil as well as of the seed. However, tumor eradication by means of radical surgery and radiotherapy is still the treatment of choice in cancer of the breast. All tumors considered curable by accepted methods of therapy must not be deprived of this treatment in favor of experimental measures.

Review of the Literature

Estrogens

The administration of sex steroids to upset the balance of hormone homeostasis is the converse of castration therapy, suggested more than fifty years ago. Long before the work of Lathrop and Loeb[11] and Lacassagne,[12] or the identification and isolation of the estrogens by Doisy[13] and Butenandt,[14] the ovary with its hormones was suggested as the organ of evil influence in breast cancer. In 1896 Beatson[15] stated "that we must look in the female to the ovaries as the seat of the exciting cause of carcinoma, certainly of the mamma." Shortly thereafter, in 1900, Boyd[16] described the benefits of oöphorectomy in cancer of the breast.

In 1935 Haddow and his co-workers noted that some carcinogenic hydrocarbons retarded the growth of malignant tissues. Because of their slight estrogenic activity, a therapeutic trial of estrogens in the treatment of breast cancer was planned. Haddow, Watkinson, Paterson and Koller[17] in 1944 reported on the influence of synthetic estrogens in advanced cancer. During the same year the Royal Society of Medicine[18] discussed the use of estrogens in late cancer of the breast and a joint scientific committee was established in liaison with the British Empire Cancer Campaign for the purpose of group study. In this country Nathanson[19, 20] was the first to inaugurate and pursue this chemotherapeutic approach. His experience concerned the sex steroids and cancer; his clinical appraisal of stilbestrol in advanced breast cancer appeared in 1946, closely followed by the work of Herrmann, Adair and Woodard.[21]

Androgens

Primitive man believed that courage was enhanced by ample portions of a stew prepared from the heart and testes of a lion. However, it was not until the eighteenth century that John Hunter first demonstrated the hormonal potency of the testes by actual experimental methods. Almost a century later (1889) Brown–Sequard tested androgens in himself at the age of seventy-two for the purpose of rejuvenation.

"To know is science, to believe one knows is ignorance," yet science waited until McGee, Juhn and Domm[22] in 1928 first isolated a pure androgen from animal testes before the empirical observations of "believers" and "make-believers" in endocrinology ceased and basic steroid biochemistry began. When Loewe, Voss, Lange and Wähner[23] first demonstrated in 1928 the presence of a urinary androgen, real progress in the chemistry of these compounds commenced. The work of Butenandt (1931–1932),[24] Ruzicka (1934)[25] and David, Dingemanse, Freud and Laqueur (1935)[26] soon culminated in the synthesis of pure testosterone.

The first clinical report of androgenic therapy in metastatic or advanced breast cancer was that of Loeser (1939).[27] The manifestations of the male sex hormone were initially noted as incidental findings, but the results were sufficiently striking to be appreciated as significant. Ulrich[28] at about the same time reported similar tumor regression in two patients, one of whom was benefited by both castration and the concomitant use of testosterone. Subsequent reports by Loeser (1941),[29] Farrow and Woodard (1942),[30] Fels (1944),[31] Prudente (1945),[32] and Adair and Herrmann (1946),[33] were carefully reviewed in a noteworthy paper by Adair (1947)[34, 35]; they indicated that the influence of testosterone in breast cancer was striking even if uncertain.

Clinical Study

Recently the promotion of medical progress by the co-ordination of the sister sciences has been emphasized. Large research programs, with planning for co-operative discovery, were among the valuable medical developments of World War II. The organization of collaborative clinical research by the teamwork of medical investigators all with one principal interest was reinforced by the overlapping and convergence of scientific advance on many fronts. Among the specific advantages that accrued from such cross-fertilization and pooling of clinical material was a study sponsored by the Committee on Research of the Council on Pharmacy and Chemistry of the American Medical Associa-

tion.[36] The co-ordinating Subcommittee on Steroids and Cancer was formed in 1947 to investigate and appraise the value of steroid hormones in advanced breast cancer. In reporting on this group of eighty patients with *inoperable*, *metastatic* or *recurrent* breast cancer who have received either single or multiple courses of sex-steroid therapy we acknowledge the privilege of participating in this collaborative clinical investigation.[37]

TABLE 1. *Criteria for Steroid Therapy in Advanced Cancer of the Breast.*

All cases considered for this study are unsuitable or beyond help of usual methods of treatment.
Androgen therapy
Cases of bone or soft-tissue lesions regardless of patient's age
Estrogen therapy
Postmenopausal cases regardless of patient's age
L.M.P. five years prior to treatment
Artificial menopause six months prior to treatment
Atrophic vaginal smear after pelvic surgery
Cases not admitted to special study
Castrated (either by surgery or x-ray) within preceding six months
Radiotherapy to primary or metastatic lesions within preceding six months

The criteria for steroid therapy in advanced breast cancer (Table 1) were set up by the Committee on Research; only those cases that conformed to the prescribed criteria were selected for analysis. Every patient admitted to this study had the diagnosis of cancer confirmed by biopsy prior to treatment. Biopsies subsequent to sex-steroid therapy were taken when feasible at regular intervals. In the study of the relation of sex steroids to breast cancer every possible extrinsic factor influencing the clinical experiment must be eliminated. Thus, all patients who either had had an artificial menopause or had received irradiation within the preceding six months were not considered acceptable candidates for this study. The measure of steroid effect was based on carefully recorded subjective and objective changes reviewed by a panel of consultants; thus such imponderables as the personal equation were reduced to a comparative minimum. All patients reported in this study received steroid therapy alone for a minimum period of three months. During the course of this clinical investigation a few patients received a total dose of testosterone in excess of 20,000 mg. over a period of eighteen months or more. Patients receiving two or more steroids simultaneously were excluded as unsuitable for analysis. However, since some patients received two or more hormones successively, each period of hormone administration was treated as a separate case report. Thus, in the present study 80 patients comprised a total of 97 case reports.

The dose of testosterone propionate was administered intramuscularly three times a week and varied in accord with one of four schedules: schedule A — 25 mg. three times a week; schedule B — 50 mg. three times a week; schedule C — 100 mg. three times a week; or schedule D — 200 mg. three times a week.

The dose of estrogens was administered orally and varied according to one of three schedules: ethinyl estradiol — 3 mg. daily; diethylstilbestrol — 15 mg. daily; or T.A.C.E. (tri-para-anisyl-chloroethylene) — 24 mg. daily.

Steroid hormones, as we now know them, are not a "cure" for breast cancer, but they do offer some profound and gratifying results in cases beyond the scope of surgery or radiotherapy. Many patients with bone metastases, particularly to the spine, have been relieved of their agony within a few days to a few weeks after the institution of steroid therapy. Even the transient rehabilitation of a forlorn and incurable cancer patient who had received no benefit from radiotherapy or surgery is an achievement in itself.

SUBJECTIVE RESPONSE

A favorable subjective response as indicated by "complete relief," "partial relief" or "slight relief" was found to occur in about 80 per cent of patients receiving testosterone propionate (Table 2). Although the response varied in the four dose schedules used, in general no one schedule appeared to be definitely superior to the others. In our limited series Schedule C (300 mg. per week) was found to be most favorable, but other workers have found a smaller dose equally effective. A therapeutic trial with orally given methyl testosterone is currently in progress; so far the effect appears to be satisfactory.

TABLE 2. *Subjective Changes in Patients Treated with Testosterone.*

	COMPLETE RELIEF	PARTIAL RELIEF	SLIGHT RELIEF	NO RELIEF	WORSE	TOTAL
Testosterone propionate (intramuscularly) (All dose schedules included)	18	15	13	5	6	57

A favorable subjective response was found to occur in about 52 per cent of patients receiving estrogens (Table 3). Cases recorded as "no change" or "worse" were considered to show an unfavorable response. Although our cases were too few in number to indicate any significant differences in the effects of the several estrogens, the Committee on Research, in a large and carefully analyzed series, found no important difference in response among many various estrogens. T. A. C. E. (tri-para-

anisyl-chloroethylene) appeared to be of less value in the few cases that we observed.

It is well to be cautious in evaluating subjective improvement, as many steroids are known to provide a remarkable sense of well-being as a part of their anabolic effect. Every surgeon is aware of the receptive mood of patients with incurable cancer. The power of hope in a hopeless disease is formidable; mere operation on a patient with advanced cancer will often result in the patient's declaring herself vastly improved.

Certain standards of subjective response are reliable, however. The relief of bone pain is a gratifying and common experience. Insomnia ceases. In place of anorexia there may appear a real relish for food. Bedridden patients may become semi-ambulatory. Patients desire to be allowed to return to work. Euphoria and increased libido replace listlessness and depression.

In our experience neither the age of the patient nor the state of the ovaries appeared to influence the subjective response. However, several factors of significance seemed to be related to both the total dose and the length of time of therapy. A favorable subjective response was noted in the androgen-treated cases in an optimum period of about three months of treatment and after 2 gm. of testosterone. In the estrogen-treated cases prolonged treatment appeared to improve the subjective response and to extend its duration, particularly in the older women. Despite this gross generalization, individual patients in both androgen-treated and estrogen-treated groups were seen to respond quickly after only a few weeks of therapy.

TABLE 3. *Subjective Changes in Patients Treated with Estrogens.*

	Complete Relief	Partial Relief	Slight Relief	No Relief	Worse	Total
Ethinyl estradiol, 3 mg. daily (orally)	4	8	5	8	2	27
Diethylstilbestrol, 15 mg. daily (orally)	1	1	1	2	0	5
Tri-p-anisyl chloroethylene, 24 mg. daily (orally)	0	1	0	3	4	8
Totals	5	10	6	13	6	40

Objective Response

The critical appraisal of objective response to steroid therapy was difficult to gauge. Regression or progression was usually indicated by some measurable change in the size of a soft-tissue lesion. Perhaps a skin nodule became smaller, or a primary ulcerated breast cancer may have healed. Roentgenographic changes often indicated an unmistakable difference in the size of a pulmonary shadow, whereas resorption of a pleural effusion was frequently more difficult to determine. Whenever a favorable objective response was observed during hormone therapy, the responsible sex steroid was given credit for the effect. Even if the improvement lasted only a few months, the recorded charts indicated a favorable case response. However, it would be deceptive to suggest, for example, that 25 per cent of the cases of advanced breast cancer with bone metastases were permanently benefited by testosterone (Table 4). A favorable objective response is for the most part transient and unpredictable. Some lesions have healed and remained so, and they offered the patients prospects of a prolonged life; in others there were no signs of regression and the course of the disease continued as before.

TABLE 4. *Changes in Bone Metastases in Patients Treated with Testosterone.*

	Major Regression	Partial Regression	No Change	Progression	Acceleration	Total
Testosterone propionate (intramuscularly) (All dose schedules included)	3	5	8	14	2	32

TABLE 5. *Changes in Bone Metastases in Patients Treated with Estrogens.*

	Major Regression	Partial Regression	No Change	Progression	Acceleration	Total
Ethinyl estradiol, 3 mg. daily (orally)	0	2	1	2	0	5
Diethylstilbestrol, 15 mg. daily (orally)	1	0	2	0	1	4
Tri-p-anisyl chloroethylene, 24 mg. daily (orally)	0	0	0	2	0	2
Totals	1	2	3	4	1	11

Objective improvement in bone metastases occurred in 27 per cent of the estrogen-treated pa-

tients (Table 5) and in 25 per cent of the testosterone-treated patients (Table 4). Evidence of a favorable objective response was characterized by the x-ray appearance of recalcification and increased density in the osteolytic lesions, the apparent reformation of bone architecture and contour and the healing of pathologic fractures. Destructive bone lesions have been seen to undergo complete repair under steroid therapy, yet other bone lesions present at the same time in the same patient have continued to progress apparently unchanged.

Soft-tissue changes represent an inclusive category; they comprise the response of lung lesions, of the primary tumor and of lesions of the skin and lymph nodes. In the estrogen-treated patients, 32 per cent revealed objective regression (Table 6), with perhaps the lung lesions showing the least response. In the testosterone-treated patients, 35 per cent revealed objective regression (Table 7), with little or no difference being noted between premenopausal and postmenopausal women. Testosterone appeared to be least effective in causing a regression of the primary tumor.

Since precise percentages in our modest series are sometimes scarcely justifiable, the collected cases of the Committee on Research often gave our clinical impressions, when confirmed, greater significance. Thus, in our limited experience, ethinyl estradiol seemed to be slightly superior to the other estrogens. The statistical selection of this synthetic steroid as more effective than the other estrogens was in accord with the compiled cases of the Committee, but the difference was slight and of no real significance. It was also noted in the larger series that when premenopausal patients were treated with estrogens (contrary to the protocol criteria) there was a marked acceleration of the disease and a definite decrease in objective improvement. Among the collected cases treated with estrogens it was shown that the chances of a favorable soft-tissue response were increased with the increasing age of the patient. This age differential was much less pronounced in cases treated with testosterone.

Distribution of Metastases

The distribution of metastatic lesions recorded at the beginning of steroid therapy is shown in Table 8. Although the metastatic sites appeared to be equally divided between bone and soft-tissue lesions, among patients with bone lesions there was a relatively greater tendency to favor androgenic therapy. No salient difference was noted in the individual metastatic sites in showing a favorable response to therapy. Perhaps skin and lymph-node lesions appeared to regress more readily under estrogenic influence than other soft-tissue lesions, but this was not striking. In a few patients the aggregate of metastases seemed to follow an "all or none" law in their response to steroids. This suggests that the action of hormones may take place either by direct effect on all the malignant cells, wherever they may be, or possibly by a profound general bodily alteration.

Using radioactive sodium estrone sulfate (S-35) in a tracer study of breast cancer, Lewison and

Table 6. *Changes in Primary Tumor and in Soft-Tissue Metastases in Patients Treated with Estrogens.*

	Major Regression	Partial Regression	No Change	Progression	Acceleration	Total
Ethinyl estradiol, 3 mg. daily (orally)	5	4	5	8	0	22
Diethylstilbestrol, 15 mg. daily (orally)	0	1	3	1	0	5
Tri-p-anisyl chloroethylene, 24 mg. daily (orally)	0	1	2	3	1	7
Totals	5	6	10	12	1	34

Table 7. *Changes in Primary Tumor and in Soft-Tissue Metastases in Patients Treated with Testosterone.*

	Major Regression	Partial Regression	No Change	Progression	Acceleration	Total
Testosterone propionate (intramuscularly) (All dose schedules included)	4	13	14	15	2	48

Table 8. *Distribution of Metastases in 80 Patients with Cancer of the Breast.*

Site of Metastases	Patients Treated with Estrogens	Patients Treated with Testosterone
Bone:		
Skull	4	11
Spine	6	20
Ribs and sternum	8	18
Pelvis	7	20
Femur	4	7
Other bones	0	8
Soft tissues:		
Brain	0	3
Thoracic viscera	13	18
Abdominal viscera	5	5
Skin and lymph nodes	33	45
Opposite breast	5	7

others[38] found a concentration of radioactivity in the tumor tissue that was significantly higher than could be accounted for by the random distribution throughout the body. These findings may indicate a tissue specificity of estrone sulfate for the cells of breast cancer.

Survival

During the three-year period of this steroid study a total of 80 patients were treated. Of these, 48 (60 per cent) have already died. The cause of death in most cases was progressive cancer, and autopsy findings usually confirmed the distribution of metastases as observed clinically. Additional metastatic sites were almost always found at post-mortem examination.

Although a 60 per cent mortality rate might very well be regarded as a pyrrhic victory for the sex steroids, in those cases showing a favorable objective response to therapy the average length of life was considerably longer than in those who failed to respond. Cases in which there was evidence of regression were therefore more likely to have a prolonged survival time as well as to derive palliative relief. A tendency toward a prolonged survival time was noted in the older age group, but this may be merely incidental to the natural history of the disease at this stage of life.

Table 9. *Side-Effects of Hormone Therapy in 80 Patients with Cancer of the Breast.*

	Patients Treated with Androgens		Patients Treated with Estrogens	
	no.	%	*no.*	%
Hirsutism	43	75	1	2.5
Increased libido	25	44	2	5.0
Edema	17	30	16	41
Voice change	40	70	0	0
Bleeding	2	3.5	5	13
Acne	23	40	1	2.5
Flushing	18	32	2	5
Nausea	12	21	13	33
Vomiting	6	10	10	25
Loss of hair	9	16	12	30
Pigmentation of areola	4	7	25	63
Pigmentation of axilla	4	7	21	53
Enlarged clitoris	8	14	0	0
Hypercalcemia	5	9	1	2.5
Incontinence	0	0	4	10

Side-Effects of Hormone Therapy

The sex steroids have a manifold action on a wide variety of organs in addition to their effect on breast and prostate cancer. Upsetting the neutrality of the endogenous sex steroids, as very likely occurs in the treatment of advanced breast cancer by massive doses of exogenous hormones, is probably the basis for the appearance of most of the noticeable side-effects. The incidence of the more manifest side-effects of hormone therapy is tabulated in Table 9. Most of these are well known and merit little comment; however, the more serious complications should be given careful consideration.

An increase in extracellular fluid and edema caused by the retention of salt, as noted in both androgen-treated and estrogen-treated cases, may result in congestive heart failure. Incipient cardiac decompensation and moderate edema can be adequately controlled by simple diuretic measures, a low-salt diet, ammonium chloride and digitalis when required in the poor-risk cardiac patient. Hypercalcemia, a grave complication, may occur in breast-cancer patients with bone metastases even prior to the initiation of hormone therapy, yet when it is associated with androgen or estrogen administration it most often occurs during the first few weeks of treatment and may be difficult to control. Hypercalcemia has been treated with some success by the intravenous administration of a 2.5 per cent solution of sodium citrate, but we have found the mere development of this complication to be a bad omen. Vaginal bleeding associated with estrogen therapy may occur as either a withdrawal phenomenon or as a side-effect of continuous estrogen medication. This complication caused a minimum of distress when ethinyl estradiol was the estrogen employed. One sixty-five-year-old patient bled profusely at monthly intervals while taking stilbestrol, but when estrogen therapy was changed to ethinyl estradiol no further uterine bleeding was noted. Like "morning sickness" in early pregnancy, nausea and vomiting required perseverance on the part of the patient for the continuation of treatment. The Committee on Research is now investigating other hormones that have fewer undesirable side-effects but generally retain their anticancer properties.

Discussion

Early diagnosis and immediate surgery are imperative for the patient with breast cancer that is amenable to operative treatment. Regardless of statistics, which often show the many-sidedness of truth, cancer of the breast by no means presents a hopeless proposition; it is only that there are those who have become hopeless about cancer. Notwithstanding our limited armamentarium for cancer detection, surgical intervention at the earliest possible time is the ultimate goal, but its practical accomplishment remains difficult. However, when the disease has advanced beyond the stage of operability it is provident to resort to less specific and more palliative benefits, such as x-ray or hormone therapy. Although life expectancy may be granted merely a provisional prolongation, and freedom from pain may be only a temporary mercy, yet to a patient in despair these comforts may be still a major blessing.

In this special study of sex steroids all patients treated with two or more hormones simultaneously were categorically excluded from statistical analysis. However, a limited number of "off-the-record"

observations failed to reveal any striking amelioration under this form of combined therapy. The use of testosterone propionate as a measure of prophylaxis after surgery has been favorably reported on by Prudente.[39] In many inoperable cases "extraordinary and gratifying improvement" was noted, with a prolongation of survival times. We have had no clinical experience with this form of prophylactic treatment after radical mastectomy. It is our preference, however, to reserve both castration (in the premenopausal patient) and hormones for use only when they are needed most in the event of recurrences or metastases.

Prior treatment with sex steroids seemed to have little or no influence on either subjective or objective response to subsequent therapy. In our experience those patients who failed to respond to one steroid seldom responded to another. On the other hand, those patients who responded well to the estrogens, for example, but in whom there was an eventual loss of control, usually responded well to the androgens. Thus, an occasional case could be successfully controlled by alternating courses of sex-steroid therapy.

The clinical response to the sex steroids remains unpredictable in each patient and is by no means uniform. Estrogens appear to be of greatest value in the manifestations of advanced breast cancer in older women, whereas the androgens appear to be of benefit regardless of age. The optimum dosage schedule is yet to be standardized, although in respect to the androgens 150–300 mg. of testosterone per week appears to be adequate. However, some patients have been observed to show a striking response to larger doses of sex steroids when they have failed to respond to smaller doses, the duration of therapy in both cases being identical. Objective and subjective improvement remains a matter of special sensitivity and is quite likely related to the unique steroid-hormone balance of each patient. The important problems of pellet implantation and continuous versus intermittent therapy were not investigated in this clinical experiment.

Close study of the foregoing results leads one to the disconcerting conclusion that by upsetting a patient's sex-hormone homeostasis, — whether by androgens, estrogens or castration, — one can profoundly alter a primary breast cancer or its more remote metastases. It seems quite obvious, therefore, that one of the most urgent aims of cancer research must be to discover the mode of action of the sex steroids. These hormones are the first normally produced substances to be identified that are known to have a telling effect on malignant tumors.

Summary

In this clinical study 80 female patients with advanced breast cancer were treated with androgens or estrogens for a minimum period of three months. These patients comprise a total of 97 case reports.

A favorable subjective response was noted in 80 per cent of 57 patients receiving androgens and in 52 per cent of 40 patients receiving estrogens.

Objective improvement in bone metastases was noted in 25 per cent of 32 patients receiving androgens and in 27 per cent of 11 patients receiving estrogens.

Objective improvement in soft-tissue lesions was noted in 35 per cent of 48 patients receiving androgens and in 32 per cent of 34 patients receiving estrogens.

The clinical response to sex steroids is unpredictable and without uniformity in the individual patient. The principal benefit of the estrogens appears to be in postmenopausal women, whereas the androgens may be of value regardless of age.

An adequate total dose over a sufficient length of time must be administered to make certain of an optimum response.

The sex hormones are not a "cure" for breast cancer, but they do offer profound and gratifying benefits in patients beyond the scope of surgery or radiotherapy. By enhancing the subtle influences of hormones that are normally present within the body, cancer may yet be palliated, if, indeed, not conquered.

References

1. Handley, W. S. Parasternal invasion of thorax in breast cancer and suppression by use of radium tubes as operative precaution. *Surg., Gynec. & Obst.* **45**:721-728, 1927.
2. Moore, C. H. On influence of inadequate operations on theory of cancer. *Proc. Roy. M. & Chir. Soc.* **1**:245-280, 1861.
3. Lister, J. *The Collected Papers of Joseph Baron Lister.* Vol. 2. 589 pp. Oxford: The Clarendon Press, 1909. P. 158.
4. Banks, W. M. Plea for more free removal of cancerous growths. *Liverpool and Manchester Medical and Surgical Reports* **5**:192-206, 1878.
5. Halsted, W. S. Results of operations for cure of cancer of breast performed at Johns Hopkins Hospital from June, 1889 to January, 1894. *Ann. Surg.* **20**:497-555, and *Johns Hopkins Hosp. Rep.* **4**: 297-350, 1894.
6. Meyer, W. Improved method of radical operation for carcinoma of breast. *Med. Rec. New York* **46**:746-749, 1894.
7. Wangensteen, O. H. Discussion of Bell, H. G. Cancer of breast. *Tr. Am. S. A.* **67**:27, 1949.
8. *Idem.* Discussion of Taylor, G. W., and Wallace, R. H. Carcinoma of breast. *Ann. Surg.* **132**:839-841, 1950.
9. Dunn, J. E., and Greenhouse, S. W. Cancer diagnostic tests; principles and criteria for development and evaluation. *Fed. Sec. Agency, Pub. Health Service* Pub. No. 9, Washington, 1950.
10. Cade, S. Natural history of malignant disease. *Brit. J. Radiol.* **22**: 331-341, 1949.
11. Lathrop, A. E. C., and Loeb, L. Further investigations on origin of tumors in mice. On part played by internal secretion in spontaneous development of tumors. *J. Cancer Research* **1**:1-19, 1916.
12. Lacassagne, A. Apparition de cancers de la mamelle chez la souris mâle, soumise à des injections de folliculine. *Compt. rend. Acad. d. sc.* **195**:630-632, 1932.
13. Doisy, E. A., Veler, C. D., and Thayer, S. Folliculin from urine of pregnant women. *Am. J. Physiol.* **90**:329, 1929.
14. Butenandt, A. Untersuchungen über das weibliche Sexualhormon. *Deutsche med. Wchnschr.* **55**:2171-2173, 1929.
15. Beatson, G. T. On treatment of inoperable cases of carcinoma of mamma: suggestions for new method of treatment with illustrative cases. *Lancet* **2**:104-107, and 162-165, 1896.
16. Boyd, S. On oophorectomy in cancer of breast. *Brit. M. J.* **2**:1161-1167, 1900.
17. Haddow, A., Watkinson, J. M., Paterson, E., and Koller, P. C. Influence of synthetic oestrogens upon advanced malignant disease. *Brit. M. J.* **2**:393-398, 1944.
18. Ellis, F., et al. Discussion on advanced cases of carcinoma of breast treated by stilboestrol. *Proc. Roy. Soc. Med.* **37**:731-736, 1944.
19. Nathanson, I. T. Effect of stilbestrol on advanced cancer of breast. *Cancer Research* **6**:484, 1946.
20. *Idem.* Influence of stilbestrol on advanced cancer of breast. *J. Clin. Investigation* **25**:930, 1946.

21. Herrmann, J. B., Adair, F. E., and Woodard, H. Q. Effect of estrogenic hormone and advanced carcinoma of female breast. *Arch. Surg.* **54**:1-9, 1947.
22. McGee, L. C., Juhn, M., and Domm, L. V. Development of secondary sex characters in capons by injections of extracts of bull testes. *Am. J. Physiol.* **87**:406-435, 1928.
23. Loewe, S., Voss, H. E., Lange, F., and Wähner, A. Sexual-hormonbefunde in männlichen Harn. *Klin. Wchnschr.* **7**:1376, 1928.
24. Butenandt, A. Chemical constitution of follicular and testicular hormones. *Nature* (London) **130**:238, 1932.
25. Ruzicka, L., Goldberg, M. W., Meyer, J., Brungger, H., and Eichenberger, E. Sex hormones (II): synthesis of testicular hormone and stereoisomers. *Helv. Chim. Acta* **17**:1395, 1934.
26. David, K., Dingemanse, E., Freud, J., and Laqueur, E. Über krystallinisches männliches Hormon aus Hoden (Testosteron), wirksamer als aus Harn oder aus Cholesterin bereitetes Androsteron. *Ztschr. f. physiol. Chem.* **233**:281, 1935.
27. Loeser, A. A. Male hormone in treatment of cancer of breast. *Acta Union internat. contre cancer* **4**:375, 1939.
28. Ulrich, P. Cancer bilateral — inoperable à droite — de la glande mammaire (essai d'un traitement palliatif par la castration et la testostérone associées). *Compt. rend. Soc. franç. de gynéc.* **9**:70-75 and 75-77, 1939.
29. Loeser, A. A. Mammary carcinoma response to implantation of male hormone and progesterone. *Lancet* **2**:698-700, 1941.
30. Farrow, J. H., and Woodard, H. Q. Influence of androgenic and estrogenic substances on serum calcium in cases of skeletal metastases from mammary cancer. *J. A. M. A.* **118**:339-343, 1942.
31. Fels, E. Treatment of breast cancer with testosterone propionate: preliminary report. *J. Clin. Endocrinol.* **4**:121-125, 1944.
32. Prudente, A. Postoperative prophylaxis of recurrent mammary cancer with testosterone propionate. *Surg., Gynec. & Obst.* **80**:575-592, 1945.
33. Adair, F. E., and Herrmann, J. B. Use of testosterone propionate in treatment of advanced carcinoma of breast. *Ann. Surg.* **123**:1023-1035, 1946.
34. Adair, F. E. Use of male sex hormone in women with breast cancer. *Surg., Gynec. & Obst.* **84**:719-722, 1947.
35. *Idem.* Testosterone in the treatment of breast carcinoma. *M. Clin. North America* **32**:18-36, 1948.
36. Council on Pharmacy and Chemistry, A. M. A. Estrogens and androgens in mammary cancer. *J. A. M. A.* **135**:987-989, 1947.
37. Council on Pharmacy and Chemistry, A. M. A. Estrogens and androgens in mammary cancer. *J. A. M. A.* **140**:1214-1216, 1949.
38. Lewison, E. F., Levi, J. E., Jones, G. S., Jones, H. W., Jr., and Silberstein, H. E. Tracer studies of radioactive sodium estrone sulfate (S-35) in cases of advanced breast cancer. *Cancer* **4**:537-548, 1951.
39. Prudente, A. Androgens in postoperative prophylaxis and treatment of breast cancer. *Ciba Clin. Symposia* **2**:299-306, 1950.

MALIGNANT HYPERTENSION WITH UNILATERAL RENAL-ARTERY OCCLUSION*

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AS A result of Goldblatt's studies on experimental hypertension, reported in 1937,[1] there has been a revival of interest and investigation in renal-artery occlusion as a cause of hypertension in man. In a small number of cases the occlusion has been limited to one renal artery. Although it is true that the majority of these cases cannot be diagnosed during life, autopsy study has revealed such lesions. The following case is presented as an example of malignant hypertension initiated in a young woman by occlusion of the right renal artery.

CASE REPORT

CASE 1. C. J., a 22-year-old woman, was well until the age of 19 years when, as a high-school student, she began to complain of headaches in the morning before arising and in the evening on retiring. During the succeeding 4 months she noted an increasing frequency of severe generalized headaches that were not relieved with the usual medication of aspirin, Anacin or mild sedatives. There was a gradual onset of increasing fatigability, with dyspnea on exertion. In the course of the next 2 months, immediately prior to her hospitalization, the patient noted the onset of nocturia five to six times with polyuria during the day, bouts of nausea with occasional vomiting and blurring of vision in the last 2 weeks. There had been no epistaxis or ankle edema during this time. Examination by her local physician revealed a markedly elevated blood pressure in the neighborhood of 190 100, and the patient was referred to the Boston City Hospital for study.

The patient had always lived in the vicinity of Boston. Her general health was previously good, although she was thin and never weighed over 100 lb. Childhood illnesses included measles at 6 years of age, scarlet fever at 8 years and mumps and chicken pox at intervening periods. There had been no sequelae to any of these illnesses. There was no previous history of renal infection, hypertension or heart disease. The patient's growth and development were normal. She smoked half a pack of cigarettes a day and did not drink alcoholic beverages. The family history was noncontributory.

The patient was admitted to this hospital on September 22, 1947. Physical examination revealed a thin, well-developed young woman. The temperature, pulse and respirations were normal. The average blood pressure was 200/140. The pupils were round, regular and equal, with normal reaction to light and accommodation. On ophthalmoscopic examination the disk margins were blurred bilaterally, with slight elevation of the optic-nerve heads. The retinal vessels showed spasm and narrowing of the arterioles, with arteriovenous nicking. There was a crescentic temporal choroidal tear in the right eye near the nerve head and some exudate and old hemorrhage in the left. The visual fields were normal. The ears, nose and throat were normal. There was no distention of neck veins. The chest was thin and symmetrical. The lungs were clear to percussion and auscultation. On examination of the heart the point of maximal impulse was palpated in the fifth intercostal space inside the midclavicular line. The apex beat was not visible. No murmurs or thrills were detected. There was regular sinus rhythm, with loud heart sounds over all areas. The aortic second sound was snapping and was greater than the pulmonic. Examination of the abdomen, genitalia and extremities revealed nothing remarkable. The peripheral pulses were bounding; no sclerosis of peripheral vessels was noted. There was no palpable lymphadenopathy and no peripheral edema. Neurologic examination was negative.

Laboratory examination of the blood revealed a hemoglobin of 15.5 gm. The red-cell count was 4,500,000 and the white-cell count 5560, with a normal differential. Examination of the urine revealed albumin and no sugar, acetone or bile. Urinary specific gravities ranged from 1.002 to 1.022 on random specimens. The sediment was not remarkable. A blood Hinton test was negative. The blood nonprotein nitrogen was 40 and 29 mg. per 100 cc. on two specimens. The total protein was 6.30 gm., with an albumin-globulin ratio of 3.5/2.8. The fasting blood sugar was 106 mg. per 100 cc. A stool guaiac test was negative. Urine-concentration tests (Fishberg) showed the highest concentration to be 1.017 on two occasions. The phenolsulfonphthalein excretion was 25 per cent in 15 minutes and 65 per cent in 2 hours; a repeat test showed 40 per cent in 15 minutes and 60 per cent in 2 hours. The basal metabolic rate was +12. Lumbar puncture revealed normal spinal fluid.

Blood pressures in the arms ranged from 190/130 to 240/140 and in the legs from 200/140 to 290/200. Examinations after rest, deep breathing, carotid-sinus pressure, ammonia breathing and amyl-nitrite administration showed only a slight fall, the lowest single recording being 168/118. Sodium amytal produced a fall to 158/106 and tetraethylammonium bromide in doses of 1 cc. and 3 cc. did not reduce the blood pressure below 178/130. A histamine diphosphate test showed a

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highest recording of 210/130 after a brief flush of the face. Chest and skull x-ray films and an electrocardiogram were unremarkable. Intravenous pyelogram revealed the right kidney to be smaller than the left and slightly low in position; there was prompt filling of the calyces and pelves, with good concentration of the dye.

In view of these findings it was thought that the patient had essential malignant hypertension and was a candidate for sympathectomy. It was suggested that perirenal air insufflation be withheld and that the adrenals be examined for possible pheochromocytoma at the time of operation. On October 30, 1947, a right-lumbodorsal sympathectomy was performed, with the removal of the sympathetic chain and ganglia from the level of the 8th dorsal vertebra to the 2nd lumbar vertebra, together with the greater splanchnic nerve. The adrenal gland and kidney on the right side appeared to be normal in all respects. Two weeks later the left side was operated on in a similar manner. The left adrenal gland was found to be normal in size; no examination of the left kidney at that time is recorded. The patient's convalescence was not remarkable except for the development of a left pneumothorax, which was treated successfully with aspiration. She was discharged on November 25, with a surgical girdle and elastic stockings. The blood pressure in the right arm at the time of discharge was 190/130.

During the first 3 postoperative months, the patient was confined to bed because of severe girdle pain, hyperesthesia of the abdomen and headaches. She was seen in the Out-patient Clinic on her first visit in January, 1948, 2 months after operation, at which time her blood pressure was found to be 210/180, and again in April, when her blood pressure was noted as 230/180. Chest x-ray films showed the heart to be within normal limits, with slight prominence of the left border in the region of the apex. During the next 6 months the patient was troubled with dyspnea after slight exertion and noted ankle edema, most marked toward evening. She fainted on one occasion. In May, 1948, she was started on potassium thiocyanate, 0.4-0.6 gm. daily, and a low-salt diet. In March, 1950, her physician found a blood pressure of 240/160 and started the patient on digitalis medication. An electrocardiogram taken in the Out-Patient Clinic showed the development of left-ventricular enlargement. In the month prior to her final admission she complained of increasing headaches, blurring of vision, weakness, nausea and vomiting. On the morning of admission she was seized with a severe pain in the head associated with spasm of the face; she then vomited. Examination by her physician 1 hour later revealed paralysis of the right side of the face and of the left arm, stertorous breathing and tonic and clonic convulsions. She was admitted to the Boston City Hospital in an unconscious state on March 6, 1951.

On arrival at the hospital the patient was in a deep unresponsive coma. The temperature was 99°F. and the pulse 100; respirations were of Cheyne–Stokes character, with periods of apnea up to 15 seconds. The blood pressure was 320 to 350 systolic and 140 to 180 diastolic. The skin was warm and dry. The pupils were widely dilated and fixed in the midline. The fundi showed marked tortuosity and narrowing of arterioles with ++ to +++ papilledema bilaterally. There was evidence of old hemorrhage in the left eye and recent exudate in the right. Slight neck-vein distention was present. The heart was enlarged to the left, with the point of maximal impulse in the fifth intercostal space in the anterior axillary line. There was regular sinus rhythm, with forceful heart sounds. A loud blowing systolic murmur was heard best to the left of the sternum. The aortic second sound was greater than the pulmonic. The abdomen, genitalia and extremities were not remarkable. Neurologic examination revealed complete bilateral flaccidity of the extremities. Deep tendon reflexes were hyperactive throughout, greater on the right, with moderate sustained right-ankle clonus. Plantar reflexes showed positive Babinski signs bilaterally. No response to noxious stimuli could be elicited. There was minimal nuchal rigidity. The diagnosis of intracerebral hemorrhage was made. Lumbar puncture revealed an initial pressure of 125 mm. of saline with grossly bloody fluid and xanthochromic supernatant. Urine specific gravities were 1.010 and 1.006 on two specimens. The blood nonprotein nitrogen was 40 mg.; a blood urea nitrogen on another specimen was 23 mg. per 100 cc. Within ½ hour after admission the patient became totally apneic and artificial respiration was started. Papilledema increased under observation, with new hemorrhages in the fundi. The blood pressure fluctuated between 90/60 and 140/100. She remained comatose throughout her course and died quietly on the third hospital day.

Post-mortem examination revealed no unusual external abnormalities other than well healed bilateral lumbodorsal scars. The peritoneal, pleural and pericardial cavities were unremarkable. The significant gross findings were limited to the heart, kidneys and brain, all other organs being within normal limits.

The heart weighed 480 gm. and was enlarged to the left. The left ventricle was thickened up to 3.0 cm., the myocardium being firm, homogeneous and somewhat pale on the cut surface. The right ventricle was not hypertrophied. The heart valves and chambers were normal in all respects. The coronary ostia were patent; the vessels were markedly thickened, with narrowed lumens throughout.

The right kidney weighed 100 gm.; the left 130 gm.; both kidneys were normal in shape. The surface of the right kidney was smooth except for a few minute pigmented scars. The surface of the left kidney was diffusely and finely granular, with numerous small pigmented and nonpigmented scars and pits. The left kidney was darker in color than the right. After sectioning, the architecture of the right kidney appeared normal in all respects; the corticomedullary junction was clearly defined, with the cortex measuring 0.6 cm. in width. The cut surface of the left kidney presented considerable purplish mottling; the corticomedullary junction was visible and the cortex measured 0.4 cm. in width. Petechiae were not seen in either kidney. The pelves and ureters presented no unusual findings.

On examination of the renal arteries, it was found that the aortic mouths were equally patent and normal in caliber. In the proximal portion of both vessels, as well as in the adjacent aorta, there was a slight degree of intimal thickening, with deposits of yellow atheromatous material. In the right renal artery, at a distance of 3.5 cm. from the aorta, beginning approximately at the hilus of the kidney, the vessel was narrowed in diameter with the lumen obliterated except for a central pin-point opening. A cross-section of the vessel at this point appeared firm and gray, with uniform narrowing of the diameter. This occlusion extended for a distance of 0.8 cm. and could not be separated from the vessel wall. Beyond this constriction the vessel again became patent before its major branchings within the kidney and was involved with slight arteriosclerosis. The wall of the left renal artery was thickened by opaque yellow atheromatous plaques scattered along the intimal surface. The lumen on the left side was normal in caliber.

Gross examination of the brain at the time of autopsy revealed the cerebral hemispheres to be edematous, with the greatest swelling over the right parietal lobe. The surface sulci were obliterated and the gyri markedly flattened. At the base of the brain the pons was deviated to the left, with a fairly marked cerebellar cone. The vertebral, basilar and internal carotid arteries presented a few atherosclerotic plaques. After formalin fixation, serial horizontal sections revealed the presence of massive intracerebral hemorrhage originating in the region of the right basal ganglia, destroying the thalamus, internal capsule and lentiform nucleus. Blood was seen to fill the entire ventricular system. A small localized hemorrhage was seen in the right pontine basis.

At microscopical examination, section of the right renal artery through the point of occlusion showed an over-all decrease in the external diameter of the vessel as compared with the left. The wall of the vessel was markedly thickened by collagenous fibrosis of the media. The lumen of the vessel was completely occluded by a loose connective-tissue mass through which passed small vessels of capillary size having patent lumens and containing fluid blood. The only indication of the pre-existing lumen was the persistence of the heavy internal elastic membrane buried within the organized connective tissue filling the old lumen (Fig. 1). Microscopical examination of the left renal artery showed preservation of normal architecture. There was one minor change, consisting essentially of an increase and reduplication of the internal elastic lamella. The lumen was widely patent (Fig. 2).

Examination of the right kidney revealed normal architecture in all respects. There were no scars, no lymphocytic

infiltration and no arteriolar sclerosis (Fig. 3). The left kidney presented marked focal scarring extending radially from the pyramids to the capsular surface. Within these scars there were occasional fibrosed glomeruli, atrophic tubules and an over-all slight lymphocytic infiltration. The glomeruli and tubules between the scars were well preserved. Throughout the section, and especially within the scars, there was a marked vascular change affecting the small arteries and arterioles, consisting of thickening of the vessel walls and

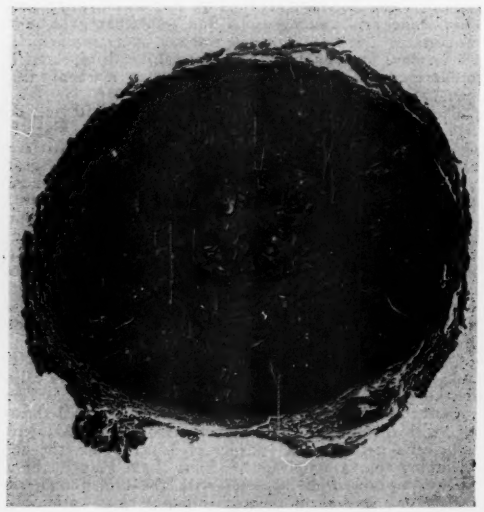

FIGURE 1. *Cross Section of the Right Renal Artery Occluded by Old Thrombus (Elastic Tissue Stain, x20).*

narrowing of the lumens. This change was consistent with the "onion-skin" effect seen in hyperplastic arteriolar sclerosis. There was no evidence of necrotizing arteriolitis or alterative glomerulitis (Fig. 4).

Microscopical study of other organs was not significant, except for a diffuse vascular sclerosis. The main left descending coronary artery was markedly thickened, showing cholesterol clefts and collagenous fibrosis of the intima. The smaller arteries and arterioles of the liver, spleen, pancreas, gall bladder, stomach, adrenal glands, uterus and ovaries showed a severe degree of hyperplastic arteriolar sclerosis such as that seen in the left kidney. There was no evidence of necrotizing arteriolitis. The pulmonary vessels were normal in appearance.

The final anatomic diagnosis was massive right intracerebral hemorrhage with ventricular extension; unilateral malignant nephrosclerosis, left kidney; right renal-artery occlusion, probably due to old thrombus; hypertensive heart disease with marked coronary arteriosclerosis; and hyperplastic arteriolar sclerosis involving liver, spleen, pancreas, gall bladder, stomach, adrenal glands, uterus and ovaries.

DISCUSSION

The well-known experimental work of Goldblatt and his associates[1] demonstrated that sustained hypertension could be produced in dogs either by partial constriction of both renal arteries or by constriction of one renal artery followed by the removal of the opposite kidney. Only a transient hypertension was produced when the renal artery of one kidney was constricted and the other left intact. Wilson and Byrom[2] and others subsequently showed that the latter procedure in rats resulted in permanent hypertension, with all its secondary sequelae. Other work performed on rabbits[3] and on goats and monkeys[4] also indicated that unilateral renal-artery occlusions were capable of at least initiating severe hypertension in these animals. Since these early experiments were made, numerous clinical cases have been reported. Freeman and Hartley[5] described the development of hypertension in a patient after the operative removal of one kidney; at autopsy the opposite renal artery was found to be sclerotic and partially occluded. Howard reported a child with hypertension due to an aneurysm of the renal artery who was cured by nephrectomy.[6] Constriction of the renal arteries by lymphosarcoma with subsequent development of hypertension was reported by Blatt and Page.[7] Another case was noted by Leadbetter and Burkland[8] in

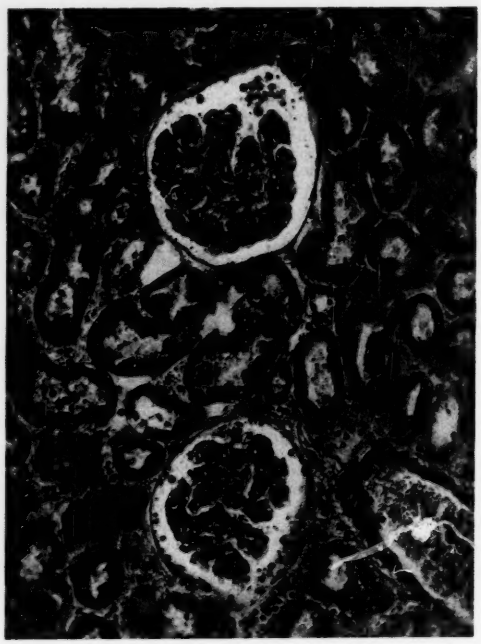

FIGURE 2. *Detail of Right Kidney, Showing Normal Afferent Arterioles Adjacent to Glomeruli (x200).*

which relief of hypertension followed nephrectomy for a smooth-muscle tumor of one renal artery. In an excellent review, Blackman[9] correlated the marked incidence of arteriosclerotic plaques in the renal arteries with severe hypertension in 50 cases coming to autopsy. Other authors[10, 11] were led to the conclusion that hypertension of unknown etiology had resulted in generalized arteriosclerosis and the accidental deposition of plaques in the renal arteries. Admittedly, a definite relation between the onset of hypertension and the presence of ar-

teriosclerotic plaques in the renal arteries is difficult to establish.

Comparatively little is known of the role of thrombosis of the renal artery in the pathogenesis of hypertension. Welty[12] analyzed the clinical features of 11 cases of renal-artery thrombosis. Hypertension was present in all. In reviewing obstructive lesions of the renal arteries, Yuile[13] presented a case of thrombotic occlusion of the left renal artery with a histologic picture of benign nephrosclerosis in the contralateral kidney. He briefly reported two additional cases of unilateral renal-artery thrombosis associated with hypertension. Fishberg reported 4 cases of embolization to one or both renal arteries, with renal infarction resulting in 3; all these patients had hypertension associated with the acute episode.[14] In one case of Boyd and Lewis,[15] partial occlusion of one renal artery was caused by a thrombus with subsequent hypertension. The removal of the abnormal kidney was followed by a return of the blood pressure to normal levels. In view of our present knowledge, it seems that hypertension may be transitory in the early congestive stages or entirely absent when total suppression of urine results. Significant hypertension more likely develops in the later stages of renal-artery thrombosis or embolism when ischemic changes in the kidney develop after recanalization of the affected artery.

In this particular case the absence of necrotizing arteriolitis in the left kidney is a reflection of the absence of renal insufficiency. This point was emphasized by Kimmelstiel and Wilson[16] in their review of cases of hypertension with malignant nephrosclerosis. The presence of marked hyperplastic arteriolar sclerosis is sufficient to establish the diagnosis of malignant nephrosclerosis in the left kidney. The complete sparing of arterioles in the right kidney strongly suggests that the constriction of the renal artery and ischemia were present on that side prior to the hypertension. The sudden onset of clinical symptoms and the rapid progression of the disease are in favor of a single etiologic factor. It seems most probable, from the nature of the lesion found at autopsy, that the right renal artery was occluded by old thrombus rather than by embolus. Biopsy of the kidneys was not performed at the time of operation, but it is doubtful that this would have altered the decision to perform a sympathectomy in this case. We do not know whether actual pulsations were felt in the renal arteries at the time of laparotomy. In retrospect, it is unlikely that any absence of pulsations could have been detected in the right renal artery beyond the point of occlusion, as the site of the obstruction was very close to the hilus of the kidney.

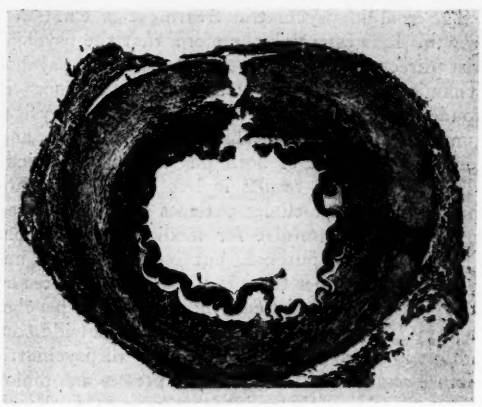

FIGURE 3. *Cross Section of the Left Renal Artery, Showing Normally Patent Lumen (Elastic Tissue Stain, x15).*

FIGURE 4. *Detail of Left Kidney Showing Hyperplastic Small Artery and Arteriole Between Glomeruli (x200).*

SUMMARY

A case of malignant hypertension is presented in which the initiating factor in the hypertension was apparently an old thrombotic occlusion of the right renal artery. There was absence of arteriolar sclerosis in the ischemic kidney with malignant nephrosclerosis on the contralateral side. The complete sparing of the arterioles of the occluded kidney makes it unlikely that the case represents essential hypertension with an incidental occlusion of the renal artery.

The literature concerning unilateral renal-artery occlusion as a cause of hypertension is briefly reviewed.

References

1. Goldblatt, H. Studies on experimental hypertension: pathogenesis of experimental hypertension due to renal ischemia. *Ann. Int. Med.* **11**:69-103, 1937.
2. Wilson, C., and Byrom, F. B. Renal changes in malignant hypertension: experimental evidence (in the rat). *Lancet* **1**:136-139, 1939.
3. Flasher, J., Drury, D. R., and Sobin, S. Persistent unilateral renal hypertension in rabbit. *Am. J. Physiol.* **158**:433-437, 1949.
4. Goldblatt, H. *The Renal Origin of Hypertension.* 126 pp. Springfield, Illinois: Charles C Thomas, 1948.
5. Freeman, G., and Hartley, G., Jr. Hypertension in patient with solitary ischemic kidney. *J. A. M. A.* **111**:1159-1162, 1938.
6. Howard, T. L., Forbes, R. P., and Lipscomb, W. R. Aneurysm of left renal artery in child five years old with persistent hypertension. *J. Urol.* **44**:808, 1940.
7. Blatt, E., and Page, I. H. Hypertension and constriction of renal arteries in man. *Ann. InMed.* **12**:1650-19, 1939.
8. Leadbetter, W. F., and Burkland, C. E. Hypertension in unilateral renal disease. *J. Urol.* **39**:611-626, 1938.
9. Blackman, S. S., Jr. Arteriosclerosis and partial obstruction of main renal arteries in association with "essential" hypertension in man. *Bull. Johns Hopkins Hosp.* **65**:353-375, 1939.
10. Oppenheimer, B. S., Klemperer, P., and Moschkowitz, L. Evidence for Goldblatt mechanism of hypertension in human pathology. *Tr. A. Am. Physicians* **54**:69-81, 1939.
11. Richardson, G. O. Atherosclerosis of main renal arteries in essential hypertension. *J. Path. & Bact.* **55**:33-39, 1943.
12. Welty, J. W. Cited by Mulholland, S. W. Hypertension's challenge to urology. *J. Urol.* **42**:957-968, 1939.
13. Yuile, C. L. Obstructive lesions of main renal artery in relation to hypertension. *Am. J. M. Sc.* **207**:394-404, 1944.
14. Fishberg, A. M. Hypertension due to renal embolism. *J. A. M. A.* **119**:551-553, 1942.
15. Boyd, C. H., and Lewis, L. G. Nephrectomy for arterial hypertension. *Am. J. Path.* **12**:45-82, 1936.
16. Kimmelstiel, P., and Wilson, C. Benign and malignant hypertension and nephrosclerosis: clinical and pathological study. *J. Urol.* **39**: 627-635, 1938.

THE ROLE OF THE INTERNIST IN A MENTAL-HYGIENE CLINIC*

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MENTAL-HYGIENE clinics are assuming a justifiably important position among community medical facilities. At some of these clinics an internist is available as a consultant. At the Veterans Administration Mental Hygiene Clinic at Hartford, the internist functions beyond the usual confines of medical consultation and recommendation. He first examined only patients in whom the question of organic disease was raised. Gradually he became integrated into the clinic and began to attend conferences and to join actively in the cooperative study of psychiatric patients, especially those suffering from psychosomatic illness. He now has a weekly session with the senior psychiatrist, at which time he may discuss psychiatric problems arising in patients under his care. Also, there is abundant opportunity for exchange of ideas, both psychiatric and medical, with the other members of the clinic staff. We believe that internal medicine has been joined with social work, psychology and psychiatry to the benefit of patients in a mental-hygiene clinic. The following are the functions of the internist as they have evolved in this clinic during the past two years: medical consultation and treatment; dispensary and supportive care; treatment of neurologic disease; orientation of patients for psychotherapy; and treatment of psychosomatic disease.

Medical Treatment of Patients Already Under Psychiatric Therapy

Problems of therapy occur in the treatment of the neurotic personality when the patient expresses symptoms referable to a body organ. It is difficult for a psychiatrist to carry on intensive psychotherapy if at the same time he is unduly concerned with the possibility of underlying organic disease. A further problem arises if the psychotherapist prescribes medication or performs physical examinations. The organic or somatic aspects of the condition may then become predominant in the mind of the patient and serve to increase resistance to intensive psychotherapy. The attention of the patient may become focused on the necessity of medical treatment rather than on the "working through" of emotional problems.

The goal in psychiatric treatment is emotional growth. It is essential, therefore, that the psychiatrist direct attention to the underlying psychodynamic factors of the neurosis. If this focus is clouded by concern about the patient's physical symptoms, it is inevitable that indecision and doubt on the part of both physician and patient will appear. This results in less effective psychotherapy. In other clinics patients may be referred to an outside internist for medical examination. This serves the purpose, but our experience has shown that at times there is a decreased interest on the part of such patients in continuing psychotherapy. This may occur because the outside consultant is often unaware of the over-all psychiatric picture and thus inadvertently expresses an opinion that coincides with, and becomes part of, the resistance of the patient to psychotherapy. When the internist is an integral part of the clinic, he is acquainted with the patient's psychiatric history and is in a better position to examine and advise without disturbing the relation of the patient to the psychotherapist.

Case 1 (No. 388). A 39-year-old man first came to the clinic in May, 1948, complaining of dizzy spells and excessive nervousness. He had had the same symptoms while in the army and on discharge had received the diagnosis of psychoneurosis, anxiety state. He also had a history of recurrent episodic nausea and vomiting since 1944 that was

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related to exacerbations of nervousness and excessive use of alcohol. He was given both group and individual therapy for treatment of his chronic anxiety.

In May, 1949, there was a sudden change in his gastrointestinal symptoms. He developed a recurrence of vomiting that was associated with severe, burning epigastric pain. He was referred to the internist, who though that a gastric ulcer had developed. An x-ray examination of the upper gastrointestinal tract was made but was reported as negative. In spite of this the patient was put on a bland diet with frequent feeding, with phenobarbital and belladonna. On this regimen he improved, only to relapse while under treatment. Since the internist had continued to follow the patient he was then referred to the Newington Veterans Administration Hospital for gastroscopy and repeat x-ray examination. Here a carcinoma of the fundus of the stomach was found and was surgically removed. The patient made a good recovery and is again under treatment at the clinic. This case illustrates our belief that easy availability of medical consultation and follow-up makes more likely the early diagnosis of organic disease complicating a psychiatric illness.

Dispensary and Supportive Treatment of Chronic Patients in Whom Intensive Psychotherapy Has Not Been Found Feasible

Some patients, after psychiatric investigation, are found not to be good candidates for intensive psychotherapy. For these patients the internist may supply dispensary and supportive care at intervals. These men apparently receive gratification of their dependency needs through the clinic and thus are helped to maintain their borderline adjustment. In a way, such patients would represent clinic failures, were it not for the fact that a realistic goal of treatment is decided on with each one. If borderline economic or social adjustment is maintained through the support of the clinic, then supportive treatment of these patients over a long period of time is a valuable function of the Mental Hygiene Clinic.

Case 2 (No. 262). A 37-year-old man was first seen at the clinic 3 years ago. He was not a good candidate for psychotherapy and did not keep regular appointments. He was hospitalized three times while in the service; the original diagnosis was simple schizophrenia. On discharge, however, he was thought to have a psychoneurosis, mixed type. He was twice a patient in Veterans Hospitals in 1946 and 1947; he had 3 admissions to state hospitals in 1948 and 1949. The consensus of medical opinion was that the patient was an inadequate person who was frequently alcoholic and who wandered from job to job living a borderline existence. In September, 1949, the patient again returned to the clinic seeking help and complaining of nervousness, irritability and insomnia. At first he was examined by the internist. The intervals between appointments were of the patient's choosing; they averaged 3 to 4 weeks. When the patient desired an appointment he would come to the clinic and would then be interviewed in the internist's first free hour, usually a day or two later. Gradually he transferred his attachment from the internist to the clinic as a whole; he is now seen by any physician who is free when the patient arrives. Treatment has consisted of accepting the patient, listening to his troubles, encouraging him to continue working and prescribing small amounts of sedative to control his periods of nervousness and insomnia.

The Treatment of Organic Neurologic Disease

The third group of patients seen by the internist comprises those with chronic neurologic disease. A complete neurologic investigation and a well supported diagnosis has been made in each case. The majority are assigned to the internist for supportive treatment and medication. However, when they have an important psychiatric problem in addition to, or associated with, their neurologic disease, they are treated by the psychiatrist.

Case 3 (No. 703). A 25-year-old veteran came to the clinic because of an alternating tremor of the right arm associated with spasticity of the right arm and right leg. The symptoms first occurred while the patient was serving with the Armed Forces but persisted and became worse after discharge. Adequate neurologic investigation had not been previously carried out; he was therefore sent to the Cushing Veterans Administration Hospital, where a final diagnosis of paralysis agitans syndrome, probably postencephalitic, was made. This man is seen at monthly intervals; his tremor and spasticity are controlled by medication, and arrangements for vocational rehabilitation have been made.

Orientation of Patients Toward Psychotherapy

Ordinarily, when patients are first referred to the clinic they are seen by the social worker (for an intake interview) and the psychologist (for projective tests); they are then referred to the psychiatrist for an intake examination. This information is presented to the clinic group at an admissions conference. A decision is then made concerning the patient's suitability for treatment and the type of therapy indicated. However, some patients are not prepared to accept psychiatric treatment, as they firmly believe that their symptoms are on an organic basis. If this belief is not seemingly given sufficient credence by the physician the tenuous thread that drew the patients to the clinic is broken, and they fail to return after one or two interviews. It is sometimes best for such patients to be referred to the internist after their social-service interview. He can then carry out an adequate medical examination and decide the importance of the organic component of the patient's complaint. This initial emphasis on the physical aspect of the complaint and the reassurance that follows complete diagnostic investigation often gives the patient confidence and alters his attitude toward the clinic. In subsequent interviews the relation between emotions and physical symptoms is stressed. This often results in the patient's becoming a favorable candidate for intensive psychotherapy by another therapist. Ideally, this orientation for psychotherapy should be carried out before the patient actually comes to the clinic, but in practice it is often necessary to accomplish this after the patient has been referred.

Case 4 (No. 698). A 28-year-old man had rheumatic fever while serving with the Armed Forces and was discharged with the diagnosis of rheumatic heart disease. He has an apical presystolic murmur indicative of mitral stenosis, but his electrocardiogram, chest x-ray films and laboratory tests have shown no evidence of cardiac enlargement or rheumatic activity. He carries on an active occupation as a route salesman for a bakery and has no dyspnea or exertional pain.

He was referred to the clinic because of recurrent stabbing precordial pains, coming on at rest, for which no organic cause had been found. When he had these pains the patient was extremely anxious and afraid that he was going to die. However, because he knew he had an organic valvular lesion

he was sure that his pain was caused by heart disease, and he was unable to accept psychiatric treatment. For this reason he was referred to the internist, who discussed the patient's cardiac status and reassured him about the normal functioning of his heart. The patient responded by symptomatic improvement, but his symptoms recurred after 2 or 3 weeks. The cycle of improvement and recurrence was repeated, but at each interview the patient was encouraged to talk about himself. While he was under treatment at the clinic a friend of his died suddenly of a heart attack; the patient's chest pain returned, with increased severity. After this, interviews elicited much more anxiety-laden material. A great fear of death became apparent; the patient stated that his pain was often worse when he went to bed, and that he assumed contorted positions as he prepared for sleep so that his body would not resemble a corpse. He began to have troubled dreams and insomnia and he became envious of people in their sixties and seventies because they had lived so long.

At this point the patient began to accept the explanation that his fear of death and anxiety might well be related to the precordial pains of which he complained. When psychotherapy was advised he was receptive to the idea; he was transferred to the care of a psychiatrist. He is now receiving intensive therapy, with good results.

The Treatment of Patients with Psychosomatic Disease

In this group, patients whose somatic symptoms predominate are often treated by the internist. There is no strict dividing line between the internist and the psychiatrist as far as the type of psychotherapy is concerned. It is a matter of degree, and it depends on the interest, aptitude and training of the therapist. The internist may use ventilation, catharsis, clarification, support and reassurance. Many patients are aware of the connection between symptoms and emotional stress, and merely pointing this out to them may be of little help. In the therapy of patients with psychosomatic complaints a combination of active medical treatment of symptoms and ample opportunity for the patient to talk about his emotional problems in a permissive atmosphere has proved effective. Occasionally, in this group of patients, problems may arise that require special psychiatric handling. Here the availability of the psychiatrist for discussion and counseling makes it possible to decide the proper course, whether it be continuation of treatment by the internist or transfer of the patient to a psychiatrist.

Case 5 (No. 756). A 42-year-old Navy veteran was referred to the clinic with a chief complaint of pruritus ani of 3 years' duration. He was discharged from naval service because of unsuitability, after having been confined to a psychiatric hospital for 3 weeks with the diagnosis of anxiety neurosis. He harbored extreme hostility toward all physicians, but especially toward service physicians — psychiatrists in particular, as he believed he had received "such a raw deal" from the latter. The mode of onset of the pruritus was not clear, but it became progressively more severe through the years. The patient was treated by numerous dermatologists with medications, diets and x-ray therapy, but to no avail. He was finally referred to the clinic by a dermatologist who had recently treated him and thought that a psychogenic element was involved. The patient's physical examination was essentially normal except for an area surrounding the anus that was markedly erythematous and edematous, with raw and crusted lesions. In addition, the patient complained of intractable constipation, relieved only by enemas. Whenever he tried to defecate normally, he had the sensation that his anus clamped down so that he was unable to pass his stool. The patient also complained of nervousness, periodic depression, irritability, insomnia and palpitation. The Rorschach test revealed a highly disturbed, neurotic, rigid man with extreme anxiety and depression. It was the opinion of the staff that he would not at first accept treatment from a psychiatrist. Consequently, the treatment was carried out by the internist under the supervision of the senior psychiatrist.

The patient was at first skeptical about deriving any benefit from treatment at the clinic. However, he was allowed to ventilate freely his repressed hostility toward all service physicians and psychiatrists. As the sessions continued, he also revealed hostility toward his co-workers and certain members of his family. In so doing he began to realize that much of his hostility was derived from suppressed aggressions — that he failed to verbalize his true feelings and so acceded unwillingly though permissively to the desires of others. He soon found it possible to say "no" on many occasions, when formerly he would not have dared to do so. At approximately this stage of therapy a marked improvement in the anal pruritus was noted, with an almost complete healing of the circumanal lesion. In addition, the constipation seemingly resolved itself, and the patient had normal daily bowel movements for the first time in years. Even more striking than the physical improvement were the personality changes. The patient felt happier, was much less tense and irritable, was able to relax more easily and established easier and better relation with others. This patient is still being seen at 3-week intervals; he has continued to be almost asymptomatic for over 4 months.

This case illustrates the type of psychotherapy that can be carried out by an internist under a co-operative clinic program.

Discussion

When the internist first joined the Mental Hygiene Clinic the sole duty outlined for him was that of medical consultation. Later, as the clinic enlarged, it became evident that the internist could be of help in treating patients whose problems were not strictly medical in nature.

We have reviewed the records of the first 100 patients seen by an internist and found that they were easily subdivided into the 5 categories described. The further breakdown of each group is as follows: medical consultation — 46 per cent of cases; dispensary and supportive care — 11 per cent of cases; neurologic care — 11 per cent of cases; orientation for psychotherapy — 7 per cent of cases; and psychosomatic care — 25 per cent of cases.

About one third of the internist's time is spent in seeing patients on one or several occasions to determine the presence or absence of organic disease. The remainder of his time is devoted to treatment. Of the treatment group, 50 per cent of the patients suffer from psychosomatic disease; the other 50 per cent comprises dispensary and neurologic cases and patients in whom further orientation for psychotherapy is necessary. It is thus evident that the internist's duties do not consist of routine physical examinations alone and that he is actively engaged in the treatment of patients.

In a co-operative psychiatric-medical arrangement such as this clinic offers, there is less chance of failure to recognize disease, either psychiatric or organic. Moreover, educational advantages are

inherent in a group in which free exchange of ideas is encouraged. Studies of patients with conditions such as peptic ulcer, ulcerative colitis, hypertension, epilepsy, headaches and so forth can be made, for extensive psychiatric data and medical observations are collated jointly. Because internal medicine, psychiatry, social work and psychology are functioning together, the psychotherapist gains confidence in his mode of treatment, the internist receives a deeper insight into the psychiatric aspects of medicine and the patient is benefited by this co-operation.

THE EFFECT OF DEPO-HEPARIN ON THE PROTHROMBIN TIME*

With Observations on the Combined Use of Heparin and Dicumarol

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THE efficacy of anticoagulant therapy in many clinical conditions has now been well established. Heparin and dicumarol have been the most widely used materials, but neither drug has proved to be entirely ideal. Heparin, on the one hand, is expensive and has a relatively short duration of action, which makes its prolonged administration cumbersome and expensive. Dicumarol, on the other hand, has the advantage of being inexpensive, but the delay in its onset of effect may be a great disadvantage under certain circumstances. As a general rule, when an anticoagulant is indicated, an immediate as well as a prolonged effect is desirable. For this reason, a program combining heparin and dicumarol is theoretically the best compromise.

In the present study we have utilized this combination by giving heparin in a base that provides for slow release of the active material (Depo-Heparin, Upjohn), with the simultaneous administration of dicumarol. It became apparent, in view of the daily prothrombin times, that heparin was significantly altering the results of the determinations. Our hospital routine provides that the withdrawal of all blood samples for daily prothrombin-time determinations be done at the same time each morning. The initial dose of the anticoagulant drug was administered at varying times as circumstances directed. This has made it difficult to prescribe safely the necessary dosage of dicumarol. Although it has been stated that the prothrombin time is not altered by usual therapeutic levels of circulating heparin when determined by ordinary methods,[2] the following clinical experiment was devised to re-examine this thesis.

Method

Six medical students in normal health, weighing over 60 kg., were selected. Two sets of control laboratory studies were carried out on separate days. The subjects were then given 400 mg. of Depo–Heparin by deep subcutaneous injection, and prothrombin and coagulation times were determined at suitable intervals. The coagulation times were performed by a modified Lee–White technic. Three tubes of uniform diameter were used. The syringes, tubes and needles were rinsed with sterile saline solution. The tubes were incubated at 37°C. The prothrombin times were determined by the Quick one-stage method and the results reported in percentage of mean normal, employing a saline-dilution curve.

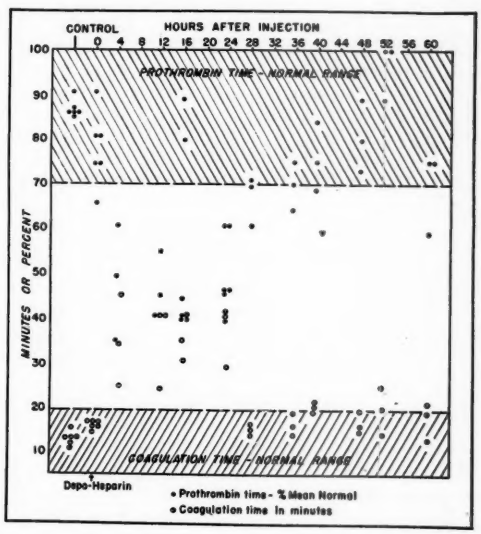

FIGURE 1. *Individual Prothrombin and Coagulation Times at Given Intervals After the Injection of 400 Mg. of Depo-Heparin.*

Results

It is apparent from Figures 1 and 2 that in each case the prothrombin times were markedly affected

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by the administration of Depo–Heparin alone. Moreover, there was only a rough and inconstant relation between the elevation of the coagulation time and the elevation of the prothrombin time. This effect became manifest within four hours after the injection of Depo–Heparin; it was most marked twelve hours after injection and persisted for twenty-four to twenty-eight hours in some cases.

The volunteers were ambulant throughout the experiment period; it is of interest that they all experienced marked local pain, tenderness, heat and induration at the site of injection. There was,

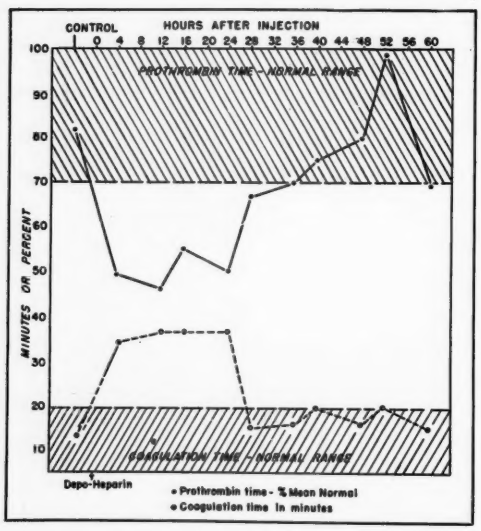

FIGURE 2. *Arithmetical Mean of Individual Prothrombin and Coagulation Times After Injection of Depo-Heparin.*

as well, a moderately severe systemic reaction in all cases, with malaise and with fever ranging between 101° and 103°F. The onset of the systemic symptoms was noted eight to twelve hours after the injection. Several subjects developed chills, myalgia, nausea, vomiting and diarrhea. This phenomenon was repeated in one case when a different lot of the drug was used. However, this same lot did not produce any of these manifestations in hospitalized patients. In our experience, these untoward symptoms have not been noted in the usual hospital patient confined to bed. It may therefore be related to activity.

DISCUSSION

Long, Hurn and Barker[1] noted the ability of sodium heparin administered intravenously to elevate the prothrombin time; they suggested that blood samples for prothrombin times should not be drawn for at least three hours after intravenous injection. Others[2] have stated that, within the therapeutic range, the prolongation of the coagulation time by heparin has no significant effect on the prothrombin time. Smiles[3] has described the combined use of Depo–Heparin and dicumarol and apparently has had no difficulty in adjusting the daily dosage of dicumarol under these conditions.

It is generally accepted that dicumarol has no inhibitory action on blood clotting in vitro. Its action is chiefly, if not solely, due to suppression of prothrombin formation in the liver. The exact site of the anticoagulant mechanism of heparin, on the other hand, has not been definitely established. It does interfere with the reactions of the coagulation mechanism at some point in the "first stage," that is, before the conversion of fibrinogen to fibrin. Most observers believe that it enters somewhere at the thromboplastin, AC-globulin or "plasma-antithrombin" level. Most probably the mechanism occurs by interference with a combination of these components. Howell[4] postulated that heparin combines with prothrombin to form a complex from which heparin can be removed by an excess of thromboplastin. Riggs[5] suggests that heparin prevents the formation of thrombin by combining directly with thromboplastin to prevent the activation of prothrombin. It has been stated[6] that the antagonism between heparin and thromboplastin is mutual and quantitative and that an excess of either nullifies the action of the other. We have made no extensive attempts to explain the mechanism of the effect of heparin in increasing the prothrombin time when determined in the previously described fashion. However, because of the possible interaction of heparin and thromboplastin, several parallel prothrombin-time determinations (Quick method) were carried out in which double the amount of the usual thromboplastin excess was added. This produced no significant deviation in the results. This therefore suggests that it alone is not the mechanism for the influence of heparin. The effect on the prothrombin-time laboratory determination may be presumed to be due largely to the inactivation of plasma AC globulin.

Because of the difficulty in determining the daily requirements of dicumarol under the circumstances of this phenomenon, we have found it more feasible to employ either intravenous or deep subcutaneous administration of sodium heparin. In this way the prothrombin time can be determined at the interval of choice and dicumarol may be given as needed. The potential hazards of waiting for a relatively long period of time for the heparin effect to become dissipated are thus obviated. The potentiation of the anticoagulant effect when the two drugs are used simultaneously has been shown.[7] Because of the probable increased effect of combined therapy on the actual clotting mechanisms of the body, any attempts to give dicumarol in the face of an

increased prothrombin time would be reprehensible. We must admit that we have no idea of the *true* coagulant state of the blood in any given case from laboratory methods now commonly used.

Conclusions

A small clinical study has been reported in which an attempt has been made to determine the effect of the administration of Depo–Heparin on the prothrombin time of blood in normal persons.

In each case the prothrombin times were significantly increased, but in an inconstant fashion.

It is suggested that either the intermittent intravenous or the deep subcutaneous methods of administering sodium heparin are more satisfactory than the use of Depo–Heparin when combined dicumarol anticoagulant therapy is indicated.

The importance of drawing blood samples for prothrombin-time determinations at suitable intervals after heparin injection is again emphasized.

References

1. Long, M., Hurn, M., and Barker, N. W. Effect of heparin on prothrombin time. *Proc. Staff Meet., Mayo Clin.* **21**:225-229, 1946.
2. Jaques, L. B. Fundamental consideration of anticoagulant therapy. *New Eng. J. Med.* **243**:395-401, 1950.
3. Smiles, W. J. Long-acting heparin preparation: useful adjunct in anticoagulant therapy; clinical trial of depo-heparin sodium in 15 cases. *U. S. Armed Forces Med. J.* **2**:45-51, 1951.
4. Howell, W. H., and Holt, E. Two new factors in blood coagulation-heparin and pro-antithrombin. *Am. J. Physiol.* **47**:328-341, 1918.
5. Riggs, D. S. Anticoagulants. *New Eng. J. Med.* **242**:179-183, 1950.
6. Ferguson, J. H. Heparin and plasma albumin in relation to thromboplastic action of trypsin, cephalin and brain extracts. *Proc. Soc. Exper. Biol. & Med.* **42**:33-37, 1939.
7. Walker, J., and Rhoads, J. E. Effect of dicumarol on susceptibility to action of heparin. *Surgery* **15**:859-865, 1944.

MEDICAL PROGRESS

THE ARTIFICIAL KIDNEY

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THE opening paragraph of the first published work on the artificial kidney reads as follows:

> There are numerous toxic states in which the eliminating organs of the body, more especially the kidneys, are incapable of removing from the body, at an adequate rate, the natural or un-natural substances whose accumulation is detrimental to life. In the hope of providing a substitute in such emergencies, which might tide over a dangerous crisis, as well as for the important information which it might be expected to provide, concerning the substances normally present in the blood, and also for the light that might thus be thrown on intermediary stages of metabolism, a method has been devised by which the blood of a living animal may be submitted to dialysis outside the body and again return to the natural circulation without exposure to air, infection by micro-organisms, or any alteration which would necessarily be prejudicial to life.[1]

It remains today an entirely adequate statement of the ends to be attained by workers in this field.

Its authors, Abel, Rowntree and Turner, had successfully used their device a number of times when they made their preliminary report in May, 1913. Their apparatus (Fig. 1) was an elaborate one, consisting of collodion tubes, which they formed and extruded themselves, that acted as the semipermeable membrane and were tied to a system of branching glass tubes with string. In order to prevent coagulation of the blood during its course outside the body they employed hirudin, the active anticoagulant of the leech. Appalled by the price of commercially manufactured hirudin, they undertook to buy, from "cupping barbers in France," leeches at $6.00 per 100. Carefully decapitating the leeches, they ground the heads in saline solution and extracted the hirudin from the solution. Their rinsing fluid, into which diffusible substances passed from the blood by way of the collodion membrane, was 0.6 per cent sodium chloride. As the

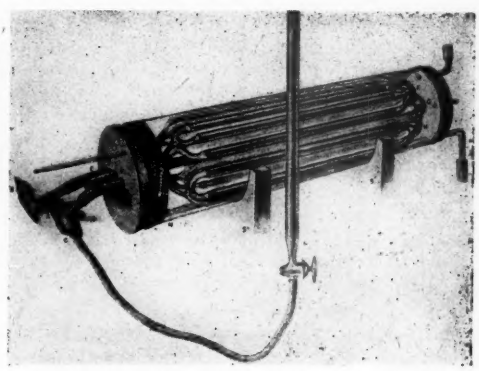

Figure 1. *Perspective View of Vividiffusion Apparatus (Earlier Form with Sixteen Tubes).*

A, *arterial cannula;* B, *venous cannula;* C, *side tube for introduction of hirudin;* D, *inflow tube;* E, *outlet tube;* F, G, *supporting rod attached at* H *and* K *to branched U-tubes;* L, *burette for hirudin;* M, N, *tube for filling and emptying liquid in outer jacket;* O, *air outlet;* P, *dual branching point of inflow tube;* Q *and* R, *quadruple branching points of same;* S, S′, *wooden supports;* T, *thermometer. At points* H *and* K *the blood is collected from four tubes into one, bending around to the back and there redividing into four return-flow tubes. (Reprinted with permission of the publisher from Abel, Rowntree, and Turner.*[2])

apparatus could not be sterilized by heat, it was kept sterile by filling it with thymol between experiments.[2] In spite of the difficulties obviously

*Established investigator, American Heart Association; associate in medicine, Peter Bent Brigham Hospital; instructor in medicine, Harvard Medical School.

involved, they took their dialyzer to London in the summer of 1913, where its demonstration was "warmly applauded."[3] They were able to remove toxic substances such as salicylate from the blood with ease, and they described in some detail the fractionation of the rinsing fluid to isolate the various nonprotein constituents of the blood that had accumulated in considerable quantity by diffusion from the animal's circulating plasma.[4]

Von Hess and McGuigan[5] modified Abel's original technic in 1914 and used it for the study of the condition of sugar in the circulating blood. Van der Heyde and Morse[6] and Love[7] in 1920 attempted to improve the collodion membranes of Abel and, drawing heavily on the natural resources of the animal kingdom, employed fish bladders, the intestines of the cat, rabbit, turkey and, to best advantage, the chicken to modify and substitute for the more delicate collodion membrane. The technical difficulties of these early apparatuses made impossible their clinical application and apparently discouraged other investigators until the report of Necheles in 1923.[8] This author constructed an apparatus that used as the semipermeable membrane Goldschlägerhaut (goldbeater's skin made of animal peritoneum). Tubes of this membrane were placed between nets of wire, which served to prevent expansion. Necheles, too, used hirudin as an anticoagulant. In experiments with nephrectomized dogs, he noted improvement in apathy after dialysis in 2 experiments that were continued for about two and a half hours of dialysis. The author noted that the life of a nephrectomized animal was not appreciably prolonged by dialysis, although there was marked improvement in the symptoms immediately after the procedure. The improvement, however, was less marked with successive dialyses. Present-day workers in the field have made similar observations. Necheles suggested the use of this apparatus in patients with temporary anuria. Three years later he had shifted his base of operations to Peking, where, apparently finding Chinese Goldschlägerhaut suitable, he used his dialyzer, in collaboration with Lim, to isolate a gastric secretory excitant from the blood of recently fed dogs.[9] This substance was found in the dialysate in appreciable amounts when blood from the portal circulation was dialyzed. In a subsequent paper,[10] Necheles described in further detail his apparatus and the results of its application to nephrectomized dogs. It is of interest that the pump that he describes in his publication is identical with the one used today in this laboratory, with the exception that instead of the rubber membrane one made of a plastic material is used.

Necheles exhibited a surprising degree of versatility, and the atmosphere of Peking must have been conducive to expansion, for in the same journal two months later there appear articles by this author on the construction of a lens for an artificial eye[11] and on the causes of night activity in some insects.[12] The former deals with an adaptable lens for an artificial eye, constructed of glycerin and condom rubber. The latter included, among other reflections, speculations on why the cockroach flees from light.

Although Howell[13] had isolated heparin in 1918, this report of Lim and Necheles is the first reference to its use for preventing coagulation during dialysis of the blood outside the body. Apparently it was not totally satisfactory, as hirudin was also employed.

Haas, who had used a collodion-tube system previously,[14, 15] published the results of his work in 1935 with the conclusion that the method was not altogether satisfactory.[16] In this country, Thalhimer[17] employed heparin that had been purified[18] sufficiently to be injected intravenously in human beings with safety, and devised an apparatus in which the semipermeable membrane was for the first time made of cellophane. This cellophane membrane was the same seamless sausage casing that is utilized in many apparatuses in use today. The author noted the removal from nephrectomized dogs of 700 mg. of urea nitrogen in a three- to five-hour dialysis. He compared these results to those of exchange transfusion with a normal animal and, finding the latter more satisfactory, concentrated his efforts on this,[19] as Nyiri had done some time previously.[20] Some authors today[21, 22] still hold to Thalhimer's point of view.

Kolff,[23] working in Holland under conditions of German occupation, devised what must be considered the first artificial kidney to have met with any degree of clinical success. He described the construction of this apparatus and his clinical experience with it in a series of subsequent publications.[24-27] Alwall in Sweden[28] and Murray in Canada,[29] working independently, devised and described in 1947 studies made with a type of dialyzer somewhat different in construction from that of Kolff that was capable of ultrafiltration as well. Alwall has published a series of careful observations of physiologic importance,[28, 30-43] and Murray has elaborated on his clinical experience in two subsequent publications.[44, 45] Skeggs and Leonards[46] described in 1948 an artificial kidney in which the blood was contained by flat sheets of cellophane that were in turn compressed by longitudinally corrugated rubber pads through which the bath fluid flowed in a current counter to that of the blood. Muirhead and Reid[47] have described an "artificial kidney" in which urea is adsorbed onto cation- and anion-exchange resins as blood from the experimental animal passes over these columns. This interesting idea is hardly practical in its present stage, at either laboratory or clinical level.

The majority of dialyzers in use today derive from, and continue to resemble, one of the three types described above (Kolff, Alwall–Murray,

Skeggs and Leonards). About 45 such dialyzers are in use today, in laboratories and clinics in this country and Canada; experience with them and with similar apparatuses in Europe is by now sufficient to permit the drawing of conclusions about their efficacy in experimental and therapeutic medicine.[48-88]

The Dialyzing Principle

Although as late as 1947 a semipermeable membrane of animal origin[88] was used, the material commonly employed today, either in sheet form or as seamless tubing, is cellophane. Commercial cellophane is a membrane of pure cellulose containing glycerol or a similar softening agent and a small percentage of water. In order to utilize such a substance clinically as a dialyzing membrane, it is necessary that it be free of the glycerol and grossly swollen with water. When this occurs the cellophane swells to many times its original size; in this distended condition it probably contains capillary channels of submicroscopic size. It is through these channels that the molecules of diffusible substance pass from blood to bath fluid, and the size of these channels, or "the pore size" of the membrane, largely determines the size of the particles that will pass. The wall thickness of the cellophane tubing when wet is about 80 microns. Since the rate of diffusion through a membrane is roughly inversely proportionate to the square of the wall thickness, it is apparent that for efficacy a thin wall is desirable. Under dialyzing conditions the cellophane is negatively charged and probably, therefore, impedes the passage of positively charged ions. Since the electrostatic forces must decrease with a decrease in cellophane-wall thickness, this is an added reason for making these dimensions as small as possible. Thus the original composition of the cellophane, the original wall thickness and the manner of its preparation during the swelling process with water determine its porosity and its value as a dialyzing membrane. Unfortunately, commercial cellophane is prepared primarily as a packaging agent rather than as a dialyzing membrane, and its suitability for such a purpose varies from lot to lot as it comes from the manufacturer. This must be kept in mind in evaluating any statements concerning the efficacy of various types of artificial kidneys.

The cellophane membrane may be represented as dividing a vessel into two compartments. In compartment A is an aqueous solution, crystalloidal or colloidal, and in compartment B is pure water. Because of the concentration gradient across the membrane, the water will tend to diffuse into the solution and the solutes into the water compartment. If the membrane pores are large as compared with the solute particles, both processes take place at relative rates; this is "free diffusion." If, however, the pore sizes are of the same order of magnitude as the solute particles, then the solute particles are impeded in their transfer across the membrane, although transfer of the water occurs freely. In a situation in which the membrane is impermeable to the colloidal solutes but permeable to the crystalloidal solutes, a *differential diffusion* occurs. This is known as *dialysis*. If the membrane is impermeable to all solutes, so that the only diffusion is that of water into the solution, the process is ordinary *osmosis*. Such a situation, of course, results in transfer of water from compartment B into compartment A because of the osmotic pressure of the solution in compartment A. If the hydrostatic pressure is now increased in compartment A so that this pressure exceeds the osmotic pressure of the solution, there is a net flow of water *out* of the solution compartment; this process is known as *ultrafiltration*.[89] The rates of transfer in all these situations may be modified by electrostatic forces, by molecular weight and configuration, by other crystalloids in the solution and by temperature, but in general they obey the reasonably simple laws of concentration gradient, osmotic pressure and hydrostatic pressure, and as such can be roughly quantitated. This is a distinct advantage over the use of living metabolizing intestinal membranes, as in intestinal lavage, since here the transfers do not occur across inert membranes.

Preliminary attempts have been made in this laboratory to control the pore size and wall thickness of the dialyzing membranes. Such a membrane might permit more rapid passage of larger molecules. Since the toxic factors in uremia have not been specifically delineated and since current thinking places them among the larger molecules, it is possible that in addition to facilitation of the dialysis of smaller crystalloids a more specific effect on the uremic syndrome might be obtained. If this is true, the size of the apparatus might be drastically decreased and its usefulness, particularly in military medicine, greatly enlarged.

Technical Problems

"Many experiments have been made to determine the best form of apparatus combining maximum diffusing surface with minimum volume, absolute freedom from leaks, uniformity of flow, minimum exposures to surfaces of glass or other substance liable to favor clotting, etc."[1] Again, these precepts elaborated by Abel in 1913 remain today the criteria for construction of an artificial kidney.

Diffusing Surface

Such an apparatus must contain the blood in a thin film so that a large surface will be exposed for dialysis. On the other hand, the method of maintaining this thin film either by counterpressure or by rotation of a drum that tightens the membrane must obviate damage to the cellophane membranes, which must be carefully checked for leaks prior to

use. Once it is in operation, an easy method should be devised for detecting a leak, as well as an easy technic for repair or replacement of the damaged unit. Fortunately, intact cellophane is impermeable to viruses and bacteria; hence once it is sterilized it may be handled without risk of contaminating the blood within.

Flow

Uniformity of flow must be attained, as pooling along the sides or in any distended areas may favor stasis and clotting. The problem of engineering easily attainable flow through the apparatus is important not only with regard to the matter of clotting but because over-all clearances of substances from the blood by dialysis are related to flow, the clearance being greater with increased flow.[30, 71] Since the cellophane membrane is distensible, there exists a potential increase in dead space in all such apparatuses, even when they are primed before use by banked blood (the exceptions here being the ultrafilters that are filled and maintained at a constant pressure). It becomes important, then, that some form of flow control be incorporated so that shifts of blood from the patient to the machine and vice versa do not occur.

Clotting

One of the major problems involved in the use of an artificial kidney is clotting of blood in the apparatus during the procedure. Heparin is used in all cases to prevent this, but it is desirable in patients who may have bleeding tendencies to use as little as possible. Since exposure of the blood to metal or glass will favor clotting, most of the apparatuses in use today employ plastics or glass coated with silicone wherever possible. Excess turbulence of flow and rough spots or projections into the lumens of the conduits may favor defibrinization and clotting. Excess turbulence may also result in trauma to red cells, with hemolysis.

Efficacy

Although excess turbulence tends to favor clotting, a certain degree of turbulence must be present, so that through mixing of the blood avoidance of laminar flow and exposure of all particles to the membrane may be accomplished. A factor that significantly affects efficacy is the constant renewal of the thin molecular film of bath fluid immediately in contact with the outer surface of the cellophane. In the removal of urea, for instance, it is important that urea molecules that have dialyzed through the membrane be constantly removed so that fresh urea-free dialysate is in contact with the cellophane, thus assuring a maximum gradient for urea from blood to bath. For this reason it is important that there be some form of agitation of the bath fluid. The importance of this agitation and mixing in increasing the efficacy of the procedure was stressed in one of the earliest publications on the subject.[5] Agitation is accomplished in some devices by rotation of the cellophane through the dialysate on a revolving drum, in others by flow of dialysate over the cellophane in a direction counter to the blood flow within and in others by stirring the dialysate or bubbling gas through it.

Bath-Fluid Composition

In general, the bath fluid should contain normal concentrations of diffusible substances, so that transfer in either direction across the membrane will result in eventual equilibrium between blood and bath at these normal levels. The most direct effort to attain these values has been made by French workers whose bath solution comes ready-made from the Paris slaughterhouses.[90] They have solved the problem by utilizing bovine blood and plasma as a bath fluid in dog experiments with a dialyzer of small capacity. Ideally, however, the composition of the bath should take into account the needs of the individual uremic patient, in view of the fact that for any diffusible substance a higher concentration in the plasma than in the bath will result in a movement of that substance from blood to bath, provided that the membrane is permeable to such a substance. Usually the bath should contain normal plasma concentrations of the essential electrolytes and of glucose. Since only the ionized plasma calcium is diffusible, however, the concentration of calcium in the bath should attain only this value and not that of the total calcium. The pH of the bath should be as close to normal as possible. To adjust this, a bicarbonate-carbonic acid buffer system may be used by equilibrating carbon-dioxide gas with the bath containing bicarbonate. Although phosphate salts are better buffers, the uremic patient usually has an elevated serum phosphate level; hence, in order to obtain a greater blood-bath gradient for this substance, it should be omitted from the bath. Table 1 illustrates the composition of the bath fluid used at the Peter Bent Brigham Hospital. If one wishes to remove potassium rapidly in cases of hyperkalemia, potassium may be omitted from the bath for the first hour or so and then added in normal concentrations. Some attention should also be paid to the osmotic pressure or the total osmolarity of blood. If this is considerably higher than that of the bath, movement of water from bath to blood may occur, with resultant hazardous overhydration of the patient. Substances that do not cross the membrane have been used to increase the osmolarity of the bath to avoid this. Such materials as are commercially available, however, are expensive or are not of uniform molecular weight, are often contaminated with other diffusible toxic substances or make the bath so viscous that undesirable foaming occurs during the process. In addition, it is apparent that since the osmotic efficacy of a molecule varies inversely with its molecular weight,

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substances with molecules large enough to be withheld by the cellophane must, by their very nature, be less effective osmotically. The addition of glucose in high quantities to the bath was thought to be of some value for this purpose, as it was cheap and of small molecular weight, did not contribute to viscosity and was harmless if incorporated into the blood stream. Although there were preliminary claims that high concentrations of glucose in the bath fluid could be used to dehydrate the patient by causing movement of water into the bath,[26, 71]

TABLE 1. *Composition of the Bath Fluid for the Artificial Kidney.**

	gm. /100 liters of bath	*mM. /liter*	*milliequiv. /liter*
NaCl	660	113	$Na^+ = 140$
$NaHCO_3$	225	27	$K^+ = 4$
KCl	30	4	$Ca^{++} = 2.6$
			$Mg^{++} = 1.0$
$MgCl_2.6H_2O$	10.0	0.5	$HCO_3^- = 27$
$CaCl_2.2H_2O$	18.5	1.3	$Cl^- = 120.6$
Glucose	200	200 mg. per 100 cc.	

*Total osmolarity, 305 milliosmols per liter.

it is now apparent that this is not an effective way of removing water, as the glucose diffuses rapidly into the blood. Undoubtedly some transfer of water can be accomplished,[42, 71, 86] but the use of high concentrations (3 to 5 per cent) appears to have an adverse clinical effect. Another and more effective method of preventing influx of water from the bath into blood with a higher osmotic pressure is ultrafiltration. Here, by decreasing the hydrostatic pressure of the bath[28] or by increasing the hydrostatic pressure of the blood within the membrane,[46] it is possible to counteract the osmotic pressure of the blood and even to cause the passage of large amounts of ultrafiltrate from the blood. In spite of the exciting possibilities indicated by these observations of dehydrating edematous patients, it does not appear to be an effective therapeutic technic[37, 38] and may be dangerous.[82] Nevertheless, it appears that some degree of hydrostatic pressure gradient is the most effective way of maintaining water balance against the osmotic gradient. It should be emphasized that ultrafiltration *per se* is not an effective way of removing metabolites.[60] Indeed, marked hydrostatic gradients from blood to bath across the membrane actually impede the dialysis of solute. Analogous to this interesting phenomenon would be an attempt to press marbles through a sieve by constant or increasing pressure of the hand, as opposed to sifting them through by gentle agitation without pressure on the sieve's screening.

Construction

Obviously, it is desirable that an artificial kidney for general clinical use should be easily assembled for the procedure and easily taken apart for cleaning after dialysis. Optimally, all parts in contact with blood should be sterilized by steam under pressure, and, to minimize the problem of pyrogens, as many of these parts as possible should be disposable. The desirability of a small compact unit has been repeatedly emphasized in the literature. It should be stressed, however, that too often some of the criteria mentioned above are sacrificed in design for the sake of small size. This is a curious misconception. It serves to emphasize perhaps the most important concept of all—that there are entities that can never be built into an artificial kidney: the experience, knowledge and common sense of the operator.

TYPES OF ARTIFICIAL KIDNEY

It is not the purpose of this review to compare the efficacy of the various apparatuses designed for hemodialysis. Many of these differ only slightly in detail. One must consider many factors in direct comparison of efficacy in terms of metabolite removal alone. Of these, a few are: surface area, the type and preparation of cellophane, the flow through the machine, the blood-to-bath gradient and the frequency with which the bath fluid is refreshed or the amount of agitation of the bath. In only a few published observations can such comparison be made. From a clinical point of view it is questionable, whether one can directly correlate speed of dialysis with clinical improvement. In a patient with chronic uremia, one might seriously question the advisability of restoring to normal within six hours the chemical derangements that had taken months to develop. In this case, considering the compensatory physiologic mechanisms involved, it might be asked whether a less effective dialyzer applied over a longer period of time might not be of more clinical benefit.

Rotating Type

The principle of the Kolff artificial kidney, which is the prototype of many operating today, is shown in the schematic diagram in Figure 2. In spite of its bulk, this apparatus has the virtues of simplicity and effective metabolite removal. It has the added advantage of a large dialyzing area (24,000 sq. cm.). (The normal human adult kidneys have a filtering area of 7600 sq. cm.[91]) In the model at present in use at the Peter Bent Brigham Hospital, the parts in contact with the blood, with the exception of the rotating couplings and pumping valves, are completely disposable. The blood courses through the apparatus along plastic surfaces that can be sterilized by steam under pressure. The apparatus can be put together from a previously autoclaved kit in fifteen minutes. It is pertinent at this point to correct two misapprehensions that frequently confuse discussion of the Kolff apparatus. First, this machine does not rely on arterial pressure to propel blood through it. Once blood reaches the level of the rotating axle, the motion of the drum propels it through the machine and a suitable pump

returns it to a gravity feed system or to a pressure chamber and thence to the venous return. Secondly, since only a thin film of bath fluid is required for dialysis, the immersion of only half the drum in the fluid at any one time does not prevent the dialysis that occurs on the upper half of the drum, as the wire screen picks up a thin film of bath fluid that is refreshed on each loop of cellophane (literally scrubbed off) each time a segment is immersed in the bath by the downward rotation of the drum.

Apparatuses similar to this and differing only in detail have been devised by the Allis–Chalmers Company,[92] Vanatta, Muirhead and Grollman[57] and others. This rotating type of apparatus has no external support for the cellophane, hence increasing the pressure of the blood within it serves only to distend the cellophane; however, the rotary motion of the drum effectively tightens the cellophane loops, spreading the blood in a thin film at the same time that it propels it forward along the drum. Since there is little or no hydrostatic pressure within this system, such apparatuses are pure dialyzers and do not employ the principle of ultrafiltration. In spite of its bulk, this type of dialyzer is relatively simple to assemble. Recent improvements in the rotating coupling devised in this laboratory have eliminated difficulties with this part of the apparatus. In 240 trials at the Peter Bent Brigham Hospital, it has proved to be safe and effective for clinical use. Experience in 60 clinical trials made by other workers, with artificial kidneys made to specifications developed in this laboratory, has given similar results.[93-96] Satisfactory results have apparently been obtained with the Allis–Chalmers modification in 20 clinical trials[97, 98] and (after preliminary disappointment[56]) by Vanatta and Muirhead,[57] with modifications of their own design used in animal experiments. An excellent analysis of the kinetics of hemodialysis with the Brigham-modified Kolff dialyzer has recently been published.[86]

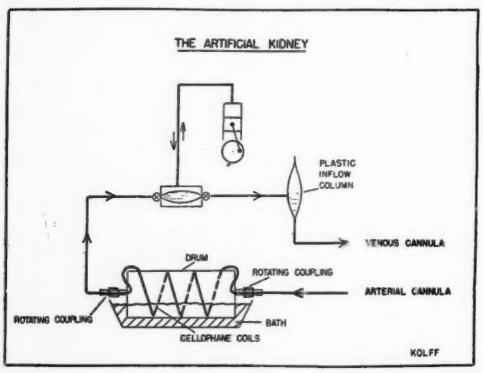

FIGURE 2. *Schematic Diagram of the Rotating Type of Artificial Kidney.*

One half of the rotating coupling is keyed to the drum; the other half is fixed and conducts blood from the artery. The two halves are opposed under spring tension and the lumen is continuous from the arterial cannula to the cellophane loops on the drum.

In the Kolff type, blood is led from the cannula in the radial artery into the apparatus and returned from the distal end by means of a pump. The patient is carefully weighed before dialysis and sedated if necessary and the predialysis chemical data taken from the arterial cannula when it has been inserted. The cannulas themselves are now made of plastic or of siliconed glass. The venous cannula is inserted first, and the patient is heparinized through this before blood flow is initiated.

With the elimination of pyrogen reactions and with adequate methods of volume control the patient has little discomfort other than that incident to the surgical procedure necessary for cannulation. Nausea and vomiting, which were common complications of earlier procedures, have been virtually eliminated by proper treatment of the cellophane and control of the bath pH. Once the flow of blood through the apparatus has been established, there is little or no subjective sensation.

The Murray and Alwall types of artificial kidneys are somewhat similar to each other in design. In these devices, the cellophane is wound in a tight coil around a supporting drum, which is grooved or constructed of screen to permit the passage of bath fluid in contact with the cellophane. In the Alwall apparatus, grooved outer casing or screen supports the cellophane tube on the other side and similarly allows passage of bath fluid between it and the outer surface of the cellophane. The Murray apparatus has no supporting screen; hence cellophane of small diameter is used to prevent a large dead space in the apparatus. The reported clinical experience with the Murray apparatus is meager.[29, 44, 45, 59] Alwall, on the other hand, has published in detail his in-vitro and in-vivo experiences with his device. The number of clinical trials exceeds 24. The apparatus itself (Fig. 3), as it is used in man, contains a dialyzing surface of only 6500 sq. cm. The osmotic pressure of the serum is balanced by dropping a tube from the bath outlet to suitable levels, thus giving an adjustable lowering of the bath hydrostatic pressure. The solution is kept constantly agitated by a motor-driven propeller. In spite of the small surface area, the clearance of metabolite is proportionately excellent and the work well conceived. An interesting touch is provided by the author's comment that the reservoir for the bath solution is placed in another room and the fluid piped warm to the apparatus through the wall. This appears to be an admirable adaptation of the methods of modern hotel organization to scientific procedure.

A dialyzer similar to the Alwall type has been made by the Westinghouse Electrical Corporation

in conjunction with this laboratory. Although clinical experience with it has been limited to date, it gives promise of being a valuable adjunct. The major difficulty with this device, as with that of Alwall,[31] is the problem of winding the cellophane between the two constricting screens. In the Westinghouse kidney, blood is pumped into the membrane and out of it into the venous return by a rotary pump. The pressure in this system can be adjusted

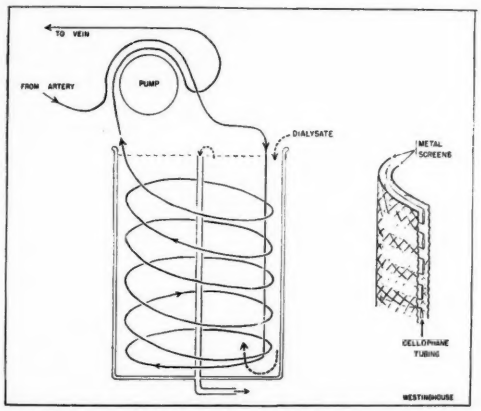

FIGURE 3. *Schematic Diagram of the Alwall Apparatus as Modified by Westinghouse.*
Coils of cellophane tubing are wound between two sets of metal screens. The rotary pump provides pressure flow through the tubing from artery to vein. In practice three such units are placed in series.

to give the desired hydrostatic pressure to the blood within the cellophane. The apparatus contains 16,000 sq. cm. of dialyzing surface, and the bath is agitated by a bubbler, which is also employed to add carbon dioxide to the bath fluid.

Skeggs and Leonards[46, 65] approached the problem by using sheets of cellophane sandwiched between corrugated rubber — later, between plastic pads. The blood is forced through the cellophane sheets while the dialyzing fluid is pumped in a counter-current flow along the outer side of the cellophane sheets between the grooves of the plastic pads. Each "sandwich" constitutes a single unit of the apparatus; a number of these are placed in parallel to give a larger dialyzing surface (Fig. 4). This apparatus, used by these authors and others in 19 clinical trials to date,[99] has apparently given satisfactory results. By evacuating the air within the tightly clamped plastic plates, an effective pressure gradient is created from the blood to the outside, thus enabling these workers to use the apparatus as an ultrafilter. As much as 2500 cc. of plasma ultrafiltrate has been removed from a dog in this manner.[82] Apparatuses operating on much the same principle have been constructed by McNeil[100] and by Lowsley and Kirwin.[79] In the former, the cellophane tubing is "sandwiched" between metal screening, the apparatus being connected in parallel and counter-current flow utilized. In the latter, both parallel and series counter-current flow types have been constructed. In both types, circular sheets of cellophane are mounted on transparent plastic supports with the blood chambers interspersed between pairs of water chambers. Only one clinical trial has been made with the McNeil apparatus,[100] and 2 cases are reported by Lowsley and Kirwin.[79] A disadvantage of the latter apparatus is that it is disinfected by soaking in cold aqueous urolocide solution prior to use rather than sterilized by steam. Sterling[66, 68, 77] has devised a basic filtration unit that consists of a sheet of cellophane be-

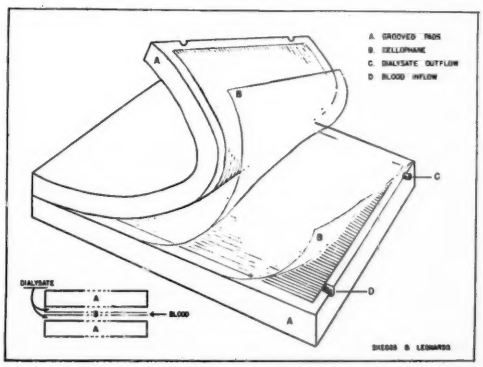

FIGURE 4. *Dialyzer as Modified by Skeggs and Leonards. In operation a spacing bar is placed between two sheets of cellophane (B) so that blood flows through these in one direction while dialysate flows on either side of the cellophane sheets in a counter-current. (Redrawn from Skeggs and Leonards.*[46])

tween paired plates forming a chamber. Blood passes through this unit on one side, perfusing fluid on the other. The artificial kidney is composed of multiple chambers held together under pressure. This apparatus, too, may be used as an ultrafilter and is autoclavable. It has been employed in 19 clinical trials to date.[101]

Kolff[76] has also constructed a stationary type of artificial kidney in which cellophane tubing is compressed between grooved plastic plates. The rinsing fluid is propelled counter-current to the blood, either by gravity or by pump. His experience leads him to believe that this is a clinically satisfactory apparatus, though less effective in terms of metabolite removal than the rotating machine.[102] The dialyzer of Rosenak and Saltzman[80] employs cellophane tubing sandwiched between flexible steel chain-linked screens. It employs counter-current flow and because of the supporting screen may be used as an ultrafilter. It is completely autoclavable

and appears to fulfill adequately the criteria stressed above. It has been used in 8 patients to date.[103] In this apparatus a vein-to-vein system is used, employing either both femoral veins or one femoral vein in which a double-lumen catheter is placed. The blood is pumped from these large-caliber veins into the apparatus and returned to an alternate vein or to an alternate channel of the double-lumen catheter. The vein-to-vein system is also employed by Skeggs and Leonards.[65]

The ion-exchange-resin artificial kidney of Muirhead[47] appears to be of little practical value at this stage of its development.

Almost without exception the apparatus in use at present, whatever its origin or variation in design, has overcome the early problems of Kolff; hence pyrogen reactions, hemolysis, clotting and shock are rare when the apparatus is skillfully handled. Experience with any of these devices has been too brief to indicate the ultimate form of the artificial kidney. Probably differing forms will exist for different purposes. Kolff's statement is reasonable: "It seems of little importance to me which type of artificial kidney is used although some investigators tend to discredit models other than their own."[76]

Clinical Usefulness of the Artificial Kidney

Experience with dialysis of the circulating blood in man has now accumulated to the point where a preliminary evaluation may be made of its value as a therapeutic tool. The following comments are based on experience in this laboratory with 210 dialyses, on data from the published literature cited above and on the recent experiences of a number of investigators who were kind enough to respond to a questionnaire.[93-104] Before undertaking such evaluations, a fundamental assumption must be made that the procedure may be undertaken with so little risk to the patient that it is a feasible therapeutic tool. This now appears to have been established, within the limits to be described below.

Indications for Dialysis

Acute renal insufficiency. Acute renal insufficiency in which the renal lesion may be deemed reversible was suggested early as an indication for use of an artificial kidney,[8] and the majority of the workers in the field today believe that it should be so used. Opposition to its use, however, has been raised by authors familiar with the treatment of acute renal insufficiency who suggest that such a procedure is not necessary.[105, 106] There can be no question that the proper management of the patient with uncomplicated acute renal insufficiency may maintain life until spontaneous recovery occurs.[107] In such cases, when the anuria is of four or five days' or even a week's duration, artificial means of removing metabolites are not "necessary." Unfortunately, despite the vigorous arguments that have been raised against its use, in many cases a number of essential points seem to have been overlooked. The first of these is that the artificial kidney, in its present stage and when properly handled, must be regarded not as a heroic terminal measure but as a *valuable adjunct to good conservative therapy.*

Much has been made of the value of high-calorie forced feeding in the treatment of this syndrome.[108, 109] Frequently, however, the severe nausea that accompanies anuria of more than a few days' duration makes such feeding difficult or impossible. An effective dialysis counts among its most striking results the abolition of, or marked improvement in, nausea and vomiting, as well as amelioration of apathy and weakness. There can be no doubt that a young, previously healthy adult may survive two or even three weeks of uncomplicated anuria with proper management. There can be no doubt, either, that the last week or ten days of his course will be difficult and uncomfortable. It is under these circumstances that the marked improvement in appetite, level of awareness and general well-being that follows dialysis becomes an important therapeutic objective, not in terms of survival alone but in terms of good general medical management.

We have learned from bitter experience that, more frequently than not, acute renal insufficiency is not an uncomplicated syndrome. Indeed, the majority of cases arise as complications of previous surgery, are superimposed on other morbid states or are secondary to the ingestion of toxins, which has other sequelae. If we choose, instead of the previous example, the situation of a 73-year-old woman, obese, arteriosclerotic and hypertensive, who has become anuric and comatose after an emergency abdominal operation, common sense dictates that such a patient should, if possible, be mobilized, made more alert and enabled to take part of her caloric intake by mouth.

Not infrequently, during continued anuria in such a patient, dialysis may achieve such results. Under such circumstances, the question whether the artificial kidney is "necessary" for survival is not pertinent. In addition, in no given case can one predict when diuresis will supervene, nor can one completely obviate, even with the best conservative therapy of prolonged anuria, the possible lethal complications such as acute spontaneous potassium intoxication, pulmonary edema, infection or pulmonary embolism. It appears wise to attempt to prevent these by mobilizing the patient and improving his general condition rather than to treat such complications when they arise. In competent hands, the artificial kidney may be of value when applied at the proper time in such cases.

The views of Frank in this regard seem pertinent, particularly since they originate in a laboratory with much experience in peritoneal lavage:

> Concerning the use of dialysis, I believe it is important to stress the fact that there is a stage of uremia which is irreversible to dialysis with the artificial kidney or to peri-

toneal lavage or to any other known method of treatment. The clinical definition of this stage may be difficult or impossible. For this reason, and because we believe the artificial kidney to be a relatively safe and highly efficient method of dialysis, we feel that its use should be early rather than too late. There is very little satisfaction to be derived from the patient who dies with normal water and electrolyte balance. The general medical profession must be educated to consider artificial dialysis as something other than last ditch heroics.[95]

Chronic renal insufficiency. The patient with chronic renal insufficiency may be well compensated except during an exacerbation of his underlying disease or when subjected to severe stress of other origin. Under such circumstances it may be possible to employ the artificial kidney with the same rationale as in acute renal insufficiency, in the belief that enough renal function may remain if the acute episode is survived to permit a reasonably useful and comfortable existence. In particular, the stress of major surgery may be too great for the patient with advanced and barely compensated renal insufficiency. The preparation by dialysis of such a patient or his treatment after the surgical procedure has been of great value in a number of cases. This is particularly true when the surgical procedure is aimed at the amelioration of renal function (pyelotomy, prostatectomy or the dilatation of urethral or ureteral strictures).

The slow, inevitably downhill course of the patient with progressive renal insufficiency who has an adequate urine volume and no vascular disease may be interrupted by dialysis when conservative measures have failed, and months or years of comfortable existence may be added in properly selected cases. Here again, experience with the selection of such cases is essential, but it is a matter of therapeutic and speculative importance that the clinical well-being following dialysis may persist for weeks or months beyond the return of blood-metabolite concentrations to predialysis levels.

Removal of toxins. The removal of diffusible exogenous toxins by dialysis was the subject of one of the first published experiments with the artificial kidney.[2] Recently the removal of acetylsalicylic acid from a human patient has been accomplished by the artificial kidney.[81] The removal of barbiturates from the circulating plasma is easily accomplished[71] and has proved to be of value in a number of cases.[110] This is particularly true of the removal of those barbiturates ordinarily handled almost entirely by the kidney, and in cases in which the intoxication is severe enough to have progressed to the stage of shock and anuria. Recently the removal of bromides in a case of chronic bromide intoxication has been presented as a feasible therapeutic procedure with the virtue of markedly shortening the clinical course of such a case when compared with previously proposed methods of therapy.[87]

Pressor Response

In about 10 to 15 per cent of the cases dialyzed in this laboratory and reported by other observers,[93-99, 101, 102] a rise of blood pressure has occurred during dialysis. Although changes of blood pressure in either direction may occur in animals and even in man with improper preparation of the cellophane,[95] this fact has been excluded as a cause of this phenomenon by observations made at the Peter Bent Brigham Hospital. In a few cases this response appears to have been of benefit when the hypotension was refractory to pressor drugs and to volume replacement of plasma and whole blood.[72, 73] The response appears to be associated with an increase in cardiac output.[111] Such an improvement in cardiac output may possibly account for the amelioration of pulmonary edema that has occurred shortly after dialysis with the artificial kidney. It has been reported from several laboratories[53, 72, 76] without change in blood volume as measured by the Evans-blue technic.[53]

Contraindications to Use of the Artificial Kidney

One of the major contraindications to the procedure is bleeding — particularly bleeding into the gastrointestinal tract. Although superficial oozing from wounds can be corrected by pressure and local hemostatic agents, the problem of fully heparinizing a patient with gastrointestinal bleeding is one that must be seriously considered in undertaking dialysis. On occasion it has been possible to give heparin to patients whose stool or vomitus was positive for occult blood without precipitating further bleeding. Serious difficulty, however, has been encountered in other cases due to the apparent initiation of persistent slow gastrointestinal bleeding during the dialysis. Bleeding into the central nervous system must be considered a possible contraindication, although we have seen only one case in which this may have played a role. Patients whose anuria is associated with acute glomerulonephritis may fail to do well in spite of excellent chemical results after dialysis. In some such patients we have seen convulsions and exacerbation of hypertension after the procedure. Since this disease is one in which the clinical course is toward healing in the majority of cases, dialysis should be undertaken for acute glomerulonephritis only when the chemical derangement seriously threatens life. Use of the artificial kidney should be postponed or avoided, if possible, in the treatment of anuria following the shock accompanying acute myocardial infarction. Although such patients have been successfully dialyzed, we have in one case seen the precipitation of a shock-like state possibly due to insufficient coronary blood flow in the presence of a stimulus to cardiac output.

Doubtful Indications

The artificial kidney may effectively correct severe chemical derangements; in cases in which the morbid state is primarily due to such derangement it should be seriously considered. Many of the patients who are considered for this procedure, however, can attribute only a fraction of their difficulty to renal insufficiency and the resulting disturbance of blood chemistry. The artificial kidney cannot correct acute pancreatitis, generalized peritonitis, pneumonia or sepsis; one must ascertain how much of the patient's problem belongs in the realm of chemical imbalance before advising dialysis. In the patient with chronic renal disease, the presence of severe hypertensive cardiovascular disease may frequently dominate the clinical picture. Such patients may show little improvement in spite of a marked drop in their blood nonprotein nitrogen. In addition, they frequently show, after dialysis, a period of oliguria; the reason for this is still obscure. Thus, even as the presence of renal insufficiency makes for unsuccessful treatment of the hypertensive state, the converse is generally true of the uremic state and its treatment with the artificial kidney. A few exceptions to this statement have been observed; as experience accumulates, it may be possible to modify this point of view. At the present time, however, the statement must stand.

Earlier workers had thought[26] that it might be possible to remove edema fluid by employing a hypertonic glucose solution in the bath or by creating a blood-to-bath hydrostatic gradient with ultrafiltration. In our experience, however, neither of these methods has been of real therapeutic use in the treatment of edema; Alwall[35] reports a similar experience. (The excellent experimental work by Leonards[82] suggests the reason for this.) Thus, although the treatment of the uremic syndrome in a patient with congestive heart failure is a perfectly safe and feasible procedure, at the present time the use of either a dialyzer or an ultrafilter to treat edema or congestive heart failure alone has not been of real benefit.

Use of the Artificial Kidney as an Experimental Tool

The value of a dialyzer as an experimental tool was realized by some of the earliest workers.[5] The ability to remove diffusible substances from the circulating blood of the living animal in normal or abnormal metabolic states has almost unlimited possibilities. In addition, the metabolic implications of the removal of one specific substance while keeping others constant and of being able to control the rate of removal is only beginning to be explored. Its use in the study of the hypertensive state developing in nephrectomized dogs,[57, 58, 85] in studying cellular transfers of potassium,[63, 64] in amino-acid metabolism,[72] in the isolation of hypertensin from the circulating blood[75] and its effectiveness in studying the relation of the cardiac arrhythmias to electrolyte imbalance[112] have delineated only a few of these possibilities.

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References

1. Abel, J. J., Rowntree, L. G., and Turner, B. B. On removal of diffusible substances from circulating blood by means of dialysis. *Tr. A. Am. Physicians* **28**:51-54, 1913.
2. Abel, J. J., Rowntree, L. G., and Turner, B. B. On removal of diffusible substances from circulating blood of living animals by dialysis. *J. Pharmacol. & Exper. Therap.* **5**:275-316, 1914.
3. International Medical Congress, Proceedings. *Brit. M. J.* **2**: 387, 1913.
4. Abel, J. J., Rowntree, L. G., and Turner, B. B. On removal of diffusible substances from circulating blood of living animals by dialysis: some constituents of blood. *J. Pharmacol. & Exper. Therap.* **5**:611-623, 1914.
5. von Hess, C. L., and McGuigan, H. Condition of sugar in blood. *J. Pharmacol. & Exper. Therap.* **6**:45-55, 1914–1915.
6. van der Heyde, H. C., and Morse, W. Modification of technic of vivi-diffusion method of Abel. *J. Lab. & Clin. Med.* **6**:520, 1921.
7. Love, G. R. Vividiffusion with intestinal membranes. *Med. Rec.* **98**:649, 1920.
8. Necheles, H. Über Dialysieren den strömenden Blutes am Lebenden. *Klin. Wchnschr.* **2**:1257, 1923.
9. Lim, R. K. S., and Necheles, H. Demonstration of gastric secretory excitant in circulating blood by vivi-dialysis. *Proc. Soc. Exper. Biol. & Med.* **24**:197, 1926.
10. Necheles, H. Method of vivi-dialysis. *Chinese J. Physiol.* **1**:69-80, 1927.
11. *Idem.* Adaptable lens for use with Kühne's artificial eye. *Chinese J. Physiol.* **1**:974, 1927.
12. *Idem.* Causes of night activity in some insects. *Chinese J. Physiol.* **1**:143-156, 1927.
13. Howell, W. H. Blood coagulation. *Am. J. Physiol.* **47**:328, 1918.
14. Haas, G. Versuche der Blutauswaschung am Lebenden mit Hilfe der Dialyse. *Klin. Wchnschr.* **4**:13, 1925.
15. *Idem.* Über Versuche der Blutauswaschung am Lebenden mit Hilfe der Dialyse. *Arch. Exper. Path. u. Pharmacol.* **116**:158-172, 1926.
16. *Idem.* Die Methoden der Blutauswaschung (dialysis in vivo). In *Abderhaldens Handbuch der Biol. Arbeitsmethoden* **8**:717, 1935.
17. Thalhimer, W. Experimental exchange transfusions for reducing azotemia: use of artificial kidney for this purpose. *Proc. Soc. Exper. Biol. & Med.* **37**:641-643, 1937.
18. Charles, A. F., and Scott, D. A. Studies on heparin: preparation of heparin. *J. Biol. Chem.* **102**:425-429, 1933.
19. Thalhimer, W., Solandt, D. Y., and Best, C. H. Experimental exchange transfusion using purified heparin. *Lancet* **2**:554-556, 1938.
20. Nyiri, W. Experimentelle Untersuchungen über gekreutzte Bluttransfusion bei Urämie. *Arch. f. exper. Path. u. Pharmakol.* **116**:117-124, 1926.
21. Snapper, I., and Schaefer, L. Treatment of two patients with hepatorenal syndrome and acute renal failure by exsanguinotransfusion. *Ann. Int. Med.* **34**:692-704, 1951.
22. Bessis, M. Use of replacement transfusion in diseases other than hemolytic disease of newborn. *Blood* **4**:324-337, 1949.
23. Kolff, W. J., and Berk, H. T. J. Artificial kidney, dialyzer with great area. *Geneesk. gids.* **5**:21, 1943.
24. *Idem.* Artificial kidney: dialyzer with great area. *Acta med. Scandinav.* **117**:121-134, 1944.
25. Kolff, W. J., and van Noordwijk, J. *De kunst matige nier* (the artificial kidney). 92 pp. Kampen, Holland: J. H. Kok, 1946.
26. Kolff, W. J. *New Ways of Treating Uremia: The artificial kidney, peritoneal lavage. Intestinal Lavage. London:* Churchill, 1947.
27. *Idem.* Artificial kidney. *J. Mt. Sinai Hosp.* **14**:71-79, 1947.
28. Alwall, N. On artificial kidney: apparatus for dialysis of blood in vivo. *Acta med. Scandinav.* **128**:317-325, 1947.
29. Murray, G. Development of artificial kidney: experimental and clinical experiences. *Arch. Surg.* **55**:505-522, 1947.
30. Alwall, N., and Norviit, L. On artificial kidney: effectivity of apparatus. *Acta med. Scandinav.* Supp. **196**:250-258, 1947.
31. *Idem.* On artificial kidney: technical and methodological problems. *Acta med. Scandinav.* **131**:237-250, 1948.
32. Alwall, N., Bergsten, B. W. B., Gedda, P. O., Norviit, L., and Steins, A. M. On artificial kidney: technique in animal experiments. *Acta med. Scandinav.* **132**:392, 1949.
33. Alwall, N., Norviit, L., and Steins, A. M. On artificial kidney: some experiences during study of dialytic treatment on animals with uremia caused by mercuric chloride poisoning. *Acta med. Scandinav.* **132**:486, 1949.
34. Alwall, N., and Herner, B. On artificial kidney: some views on indications for treatment of uremia and for active removal of oedema by means of our artificial kidney, based on studies of uremic material not treated with this method. *Acta med. Scandinav.* **132**:572, 1949.
35. Alwall, N., Norviit, L., and Steins, A. M. On artificial kidney: clinical experiences of dialytic treatment of uremia. *Acta med. Scandinav.* **132**:587, 1949.

36. Alwall, N. On artificial kidney: cases of acute renal failure with anuria-oliguria treated with excessive fluid electrolyte supply. *Acta med. Scandinav.* Supp. **229**:2-12, 1949.
37. *Idem.* On artificial kidney. *Acta med. Scandinav.* Supp. **229**:13, 1949.
38. *Idem.* On artificial kidney. *Acta med. Scandinav.* Supp. **229**:16, 1949.
39. *Idem.* On artificial kidney. *Acta med. Scandinav.* Supp. **229**:20, 1949.
40. *Idem.* On artificial kidney. *Acta med. Scandinav.* Supp. **229**:22, 1949.
41. *Idem.* On artificial kidney. *Acta med. Scandinav.* Supp. **229**:30, 1949.
42. Alwall, N., Eglitis, P., Norviit, L., and Tornberg, A. On artificial kidney: influence of saline with high glucose content on fluid balance of rabbits treated by dialysis. *Acta med. Scandinav.* **137**: 233, 1950.
43. Alwall, N., and Tornberg, A. On artificial kidney: fluid balance between blood and saline during dialytic treatment. *Acta med. Scandinav.* **138**:246, 1950.
44. Murray, G., Delorme, E., and Thomas, N. Artificial kidney. *J. A. M. A.* **137**:1596-1599, 1948.
45. *Idem.* Artificial kidney. *Brit. M. J.* **2**:887-891, 1949.
46. Skeggs, L. T., Jr., and Leonards, J. R. Studies on artificial kidney: preliminary results with new type of continuous dialyzer. *Science* **108**:212, 1948.
47. Muirhead, E. E., and Reid, A. F. Resin artificial kidney. *J. Lab. & Clin. Med.* **33**:841-844, 1948.
48. Darmady, E. M. Artificial kidney. *Proc. Roy. Soc. Med.* **41**:418, 1948.
49. Bywaters, E. G. L., and Joekes, A. M. Artificial kidney: its clinical application in treatment of traumatic anuria. *Proc. Roy. Soc. Med.* **41**:420-426, 1948.
50. Derot, M. Nouveau procédés thérapeutiques au cours des néphrites aiguës. La dialyse péritonéale. L'hémodialyse ou rein artificiel. *J. d'urol.* **53**:567-571, 1946–1947.
51. de Leeuw, N. K. M., Wener, J., and Juklicek, L. B. Use of artificial kidney in treatment of uremia. *Camsi* (Canadian Association of Medical Students and Internes) **8**:9-18, 1949.
52. de Leeuw, N. K. M., and Blaustein, A. Studies of blood passed through artificial kidney. *Blood* **4**:653-666, 1949.
53. Fishman, A. P., Kroop, I. G., Leiter, H. E., and Hyman, A. Experiences with Kolff artificial kidney. *Am. J. Med.* **7**:15-34, 1949.
54. Joekes, A. M., and Bull, G. M. Accidental hemorrhage with bilateral cortical necrosis of kidneys: treated by artificial kidney. *Proc. Roy. Soc. Med.* **41**:678, 1948.
55. MacLean, G., Ripstein, C. B., de Leeuw, N. K. M., and Miller, G. G. Use of artificial kidney in treatment of uraemia. *Canad. M. A. J.* **58**:433-437, 1948.
56. Muirhead, E. E., and Vanatta, J. C. Use of artificial kidney. *Am. J. Med.* **4**:467, 1948.
57. Vanatta, J., Muirhead, E. E., and Grollman, A. Improvements on artificial kidney: experimental study of its application to dogs bilaterally nephrectomized or otherwise deprived of renal function. *Am. J. Physiol.* **156**:443-453, 1949.
58. Grollman, A., Muirhead, E. E., and Vanatta, J. Role of kidney in pathogenesis of hypertension as determined by study of effects of bilateral nephrectomy and other experimental procedures on blood pressure of dog. *Am. J. Physiol.* **157**:21-30, 1949.
59. Lam, C. R., and Ponka, J. L. Experiences with Murray artificial kidney. *J. Lab. & Clin. Med.* **32**:1434, 1947.
60. Malinow, M. R., and Koron, W. Experimental method for obtaining ultrafiltrate of blood. *J. Lab. & Clin. Med.* **32**:461-471, 1947.
61. Merrill, J. P. Clinical application of artificial kidney. *Bull. New England M. Center* **11**:111-114, 1949.
62. Palmer, R. A., and Rutherford, P. S. Kidney substitutes in uraemia: use of Kolff's dialyser in 2 cases. *Canad. M. A. J.* **60**:261-266, 1949.
63. Reinecke, R. M., Holland, C. R., and Stutzman, F. L. Homeostasis of potassium in extracellular fluid of dog during removal by vivodialysis. *Am. J. Physiol.* **156**:290-297, 1949.
64. Stutzman, F. L., and Reinecke, R. M. Reduction of plasma potassium concentration of dog by vivodialysis and its restoration in non-visceral regions. *Am. J. Physiol.* **157**:401-403, 1949.
65. Skeggs, L. T., Jr., Leonards, J. R., and Heisler, G. R. Artificial kidney: construction and operation of improved continuous dialyzer. *Proc. Soc. Exper. Biol. & Med.* **72**:539-543, 1949.
66. Sterling, J. A., Weiss, L. B., Schneeberg, A., and Bernard, W. New type of artificial kidney: preliminary report. *Clin. Proc. Jewish Hosp.* **1**:128-130, 1948.
67. Wener, J., and de Leeuw, N. K. M. Role of potassium in dialysing fluid in treatment with artificial kidney. *Proc. Soc. Exper. Biol. & Med.* **71**:18-20, 1949.
68. Sterling, J. A., and Doane, J. C. New type of artificial kidney (preliminary clinical report). *Urol. & Cutan. Rev.* **53**:385-389, 1949.
69. Derot, M., Bernier, J. J., Legrain, M., and Pignard, P. Premiers essais cliniques du rein artificiel de Kolff. *Bull. & mém. Soc. méd. hôp. Paris* **66**:208-213, 1950.
70. *Idem.* L'hémodialyse fractionée avec le rein artificiel de Kolff. *Paris med.* **40**:145-147, 1950.
71. Merrill, J. P., Thorn, G. W., Walter, C. W., Callahan, E. J., III, and Smith, S. H., Jr. Use of artificial kidney: technique. *J. Clin. Investigation* **29**:412-424, 1950.
72. Merrill, J. P., Smith, S., III, Callahan, E. J., III, and Thorn, G. W. Use of artificial kidney: clinical experience. *J. Clin. Investigation* **29**:425-438, 1950.
73. Merrill, J. P. Present role of artificial kidney in clinical therapy. *Ann. Int. Med.* **33**:100-107, 1950.
74. Bernier, J. J. Études sur le rein artificiel de Kolff. *Semaine des hôp. de Paris* **26**: Nov. 22, 1950.
75. Kahn, J. R., Skeggs, L. T., and Shumway, N. P. Isolation of hypertensin from circulating blood of dogs by dialysis in artificial kidney. *Circulation* **2**:363, 1950.
76. Kolff, W. J. Artificial kidney: treatment of acute and chronic uremia. *Cleveland Clin. Quart.* **17**:216-228, 1950.
77. Sterling, J. A. Management of acute renal failure. *Am. Pract. & Digest Treat.* **1**:253-261, 1950.
78. Legrain, M. *Néphrites aigues anuriques.* 244 pp. Paris: G. Doin & Co., 1951.
79. Lowsley, O. S., and Kirwin, T. J. Artificial kidney: preliminary report. *J. Urol.* **65**:163-176, 1951.
80. Rosenak, S. S., and Saltzman, A. New dialyzer for use as artificial kidney. *Proc. Soc. Exper. Biol. & Med.* **76**:471-475, 1951.
81. Doolan, P. D., Walsh, W. P., Kyle, L. H., and Wishinsky, H. Acetylsalicylic acid intoxication: proposed method of treatment. *J. A. M. A.* **146**:105-106, 1951.
82. Leonards, J. R., Skeggs, L. T., Jr., and Kahn, J. R. Removal of fluid from normal and edematous dogs by means of ultrafiltration. *Federation Proc.* **10**:214, 1951.
83. Skeggs, L. T., Jr., Leonards, J. R., and Kahn, J. R. Construction and operation of apparatus for continuous ultrafiltration. Presented at a meeting of the American Chemical Society at Cleveland, April, 1951.
84. Lavik, P. S., Leonards, J. R., Heisler, C. R., and Buckaloo, G. W. In vivo dialysis as means of influencing survival of x-irradiated dogs. Presented at a meeting of the Federated Society, April, 1951.
85. Leonards, J. R., and Heisler, C. R. Artificial kidney: maintenance of life in bilaterally nephrectomized dogs and its relation to malignant hypertension. *Am. J. Physiol.* (in press).
86. Wolf, A. V., Remp, D. G., Kiley, J. E., and Currie, G. D. Artificial kidney function: kinetics of hemodialysis. *J. Clin. Investigation* **30**:1062-1070, 1951.
87. Merrill, J. P., and Weller, J. M. Treatment of bromism with artificial kidney. *Ann. Int. Med.* (in press).
88. Derot, M., Tanret, P., and Reymond, J. C. Hépatonéphrite hémolytique mortelle après ingestion de chlorate de saude: essai de traitement par l'hémodialyse (rein artificiel). *Bull. et mém. Soc. méd. d. hôp de Paris* **63**:302-305, 1947.
89. Ferry, J. D. Ultrafilter membranes and ultrafiltration. *Chem. Rev.* **18**:373-455, 1936.
90. Legrain, M. Personal communication.
91. Book, M. H. Secreting area of glomerulus. *J. Anat.* **71**:91-97, 1936.
92. Allis-Chalmers. *Time Magazine,* March, 1951.
93. Wolf, A. J. Personal communication.
94. Doolan, P. D., and Walsh, W. P. Personal communication.
95. Frank, E. D. Personal communication.
96. Rochlin, I. M. Personal communication.
97. Kearns, W. M. Personal communication.
98. Murphy, F. D. Personal communication.
99. Leonards, J. Personal communication.
100. McNeil, A., and Nakasone, N. Personal communication.
101. Sterling, J. A. Personal communication.
102. Kolff, W. Personal communication.
103. Rosenak, S. S. Personal communication.
104. Leaf, A. Personal communication.
105. Muirhead, E. E., Vanatta, J., and Grollman, A. Acute renal insufficiency. *Arch. Int. Med.* **83**:528-538, 1949.
106. Stock, R. J. Acute urinary suppression: observations in 22 patients. *Am. J. Med.* **7**:45-55, 1949.
107. Strauss, M. B. Acute renal insufficiency due to lower-nephron nephrosis. *New Eng. J. Med.* **239**:693-700, 1948.
108. Borst, J. G. G. Protein katabolism in uraemia: effects of protein-free diet, infections, and blood-transfusions. *Lancet* **1**:824-828, 1948.
109. Bull, G. M., Joekes, A. M., and Lowe, K. G. Conservative treatment of anuric uraemia. *Lancet* **2**:229-234, 1949.
110. Swan, R. C., and Merrill, J. P. Unpublished observations.
111. Merrill, J. P., and Goodale, W. Unpublished observations.
112. Weller, J. M., Merrill, J. P., and Lown, B. Unpublished observations.

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

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CASE 38011

PRESENTATION OF CASE*

A seventy-year-old woman entered the hospital because of chest pain and progressive weakness and dyspnea.

The patient had been in good health until two days before admission. Suddenly, while lying in bed, she suffered a severe crushing left-chest pain radiating down the left arm that persisted for at least twenty-four hours before it was relieved by morphine. She remained in bed but became weaker, paler and very dyspneic. She was brought to the hospital; during the ambulance ride her breathing became slow and gasping and her pulse thready.

On admission the patient was cyanotic and the respirations were 6 per minute and of gasping Cheyne–Stokes type. The pulse was thready. The pupils were contracted. The heart sounds were very faint and regular. Both lungs were almost completely filled with moist bubbling rales. There was ++ edema of the lower extremities, with marked tenderness of the right calf. The neck veins were not distended, and the liver was not palpable. Stimulants were given with only slight benefit.

The temperature was 98°F., the pulse 130 and the respirations 6. The blood pressure was 115 systolic, 80 diastolic.

Oxygen, tourniquets, Cedilanid, demerol, aminophyllin and quinidine were administered, with the result that the lung fields had cleared by the following day except for a few rales at the lung bases and some dullness and accentuation of breath sounds at the right base. The edema of the legs also disappeared.

Laboratory examination of the blood revealed a white-cell count of 12,800 and a hemoglobin of 12 gm. The urine had a specific gravity of 1.020 and gave a ++ reaction for albumin; the sediment contained 60 white cells per high power field in large and small clumps. Roentgenograms of the chest revealed prominence of the left ventricle, a tortuous aorta and diffuse soft mottling throughout both lung fields, with prominent vascular shadows. There was scoliosis of the upper dorsal spine toward the right.

An electrocardiograph (cardiette) made on admission showed a sinus tachycardia of 150; the T waves were upright in all leads except Lead CF_3, in which they were slightly inverted; the ST segment was sagging in Lead 3. The S waves were prominent in Leads 2 and 3. The QRS complexes showed low voltage in Leads 1 and 2. The Q waves were deep in the chest leads in all positions, with marked elevation of the ST segment in each lead.

An electrocardiogram made on the next day revealed a rate of 105. The QRS-complex duration was at the upper limits of normal, with most of the widening in the S phase. The CF_2 lead showed the initial ventricular deflection of QRS and a high take-off of the ST segment. There were inverted T waves in Leads CF_4 and CF_5, with absent R waves and high ST-segment take-off.

Because of the persistent calf tenderness, which at times was bilateral, a femoral ligation was considered but not done.

The patient continued to improve, but on the eighth hospital day a friction rub appeared in the precordial region, best heard in the supine position and on full inspiration, at which time a marked paradoxical pulse was evident.

Two days later, after being awakened for medication at 10:15 p.m., the patient gasped for breath. Two minutes later cardiac beats could not be heard, the corneal reflex was absent and she could not be aroused. After a few minutes she again became responsive and groaned loudly; tumultuous heartbeats were heard, with a fast and irregular rhythm. Respirations suddenly ceased, and the patient died.

DIFFERENTIAL DIAGNOSIS

DR. VICTOR G. BALBONI†: This patient entered the hospital presenting the picture of acute pulmonary edema due to left-sided heart failure. Tourniquets were applied to the extremities to reduce temporarily the return of blood to the failing myocardium; she was digitalized intravenously with Cedilanid and given demerol to quiet her. Apparently she responded to this treatment, as the pulmonary edema had largely cleared by the next day. The questions that I must answer are first, why did she suddenly develop pulmonary edema, and secondly, why did she die even more suddenly on the tenth hospital day?

In any patient with this type of severe chest pain the differential diagnosis becomes primarily one of myocardial infarction, massive pulmonary embolus and dissecting aneurysm of the aorta. In dissecting aneurysm of the aorta, pain is usually the most

*Presented at a course for graduate students in internal medicine.

†Assistant in medicine, Massachusetts General Hospital.

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characteristic feature. Customarily it is overwhelming in nature, commonly begins in the chest and almost invariably radiates — very frequently to the arms, often to the abdomen and occasionally to the legs. The pain this patient had is not very suggestive of dissecting aneurysm of the aorta, because it did not radiate except to the left arm. The dissection usually begins about 2 cm. above the aortic valve and may extend down to the abdominal aorta and even into the iliac arteries. In the process of downward dissection one or more tributaries of the aorta may be occluded, impeding the circulation to the arms or to one of the mesenteric or renal arteries. In this case, however, there is no evidence of any such train of events. Certainly cases of dissecting aneurysm of the aorta do occur in which many of these features are lacking, but the diagnosis then is made at post-mortem examination. I shall eliminate dissecting aneurysm of the aorta as a serious possibility.

Could this patient have had a large pulmonary embolus? On her entry to the hospital the right calf was described as tender; this is usually a sign of local thrombophlebitis from which an embolus might arise. The chest pain, however, was not characteristic of that associated with pulmonary embolus. In massive pulmonary embolus the initial episode is usually dyspnea and shock, with pain not a very prominent symptom. If the embolus is small and goes into one of the smaller branches of the pulmonary artery, there may be severe pain in the lateral chest wall and the patient may later raise bloody sputum. The electrocardiogram in pulmonary embolus is quite different from the electrocardiogram described here, the typical pattern being that of right-heart strain with changes in the T waves in the chest leads over the right side of the heart but not over the left side. Thus, in this case I find little to suggest pulmonary embolus other than the sudden demise and the possibility of thrombophlebitis in the legs, as indicated by the tender calves.

Finally I must consider the possibility of myocardial infarction. Here I believe all would agree that the pain was quite characteristic as regards its location, radiation and severity. The fact that a woman of her age went so rapidly into pulmonary edema with a myocardial infarction is also not unusual. The electrocardiographic findings are consistent with an anterior myocardial infarction. The slow respirations that were noted on entry to the hospital are worth commenting on. Very probably the respirations were reduced by the morphine that was given to control pain. This hypothesis is supported by the finding of contracted pupils. This is a serious situation, for the reduced respirations may result in lowering of the oxygen saturation of the blood and thus in further damage to the myocardium. It is a valid reason for giving oxygen to patients with myocardial infarction while they are receiving morphine for pain. The blood pressure of 115 systolic, 80 diastolic is fairly low for a seventy-year-old woman. Since I do not know what the blood pressure was before she became sick, I shall assume it represents a drop in blood pressure, which one would expect to find with a myocardial infarction. The clinical course was satisfactory and consistent with a myocardial infarction until the eighth day, when a precordial friction rub and a paradoxical pulse developed. Both the paradoxical pulse and the friction rub could be explained by a massive myocardial infarction and slowly disintegrating myocardium, with rupture permitting blood to leak into the pericardial sac. I interpret the episode on the day of death as due to final rupture of the infarcted myocardium. Hearts that rupture usually do so at the end of the first week; hence the time element fits this diagnosis. I shall make my diagnosis myocardial infarction with rupture of the heart.

A Physician: Do you often see prominent pulmonary arteries in the x-ray films, or is that coincidental?

Dr. John D. Reeves, Jr.: The x-ray films show pulmonary edema and severe congestion of all the pulmonary vessels. Any patient who comes into the Emergency Ward with chest pain does have a chest film to differentiate pulmonary and coronary disease. If they are well enough, we like to fluoroscope them to see if we can find a calcified coronary artery or even a pulmonary embolus.

Dr. F. Dennette Adams: Can you spot pulmonary embolus very often when it is that early? It has always been my opinion that the history of the episode is the most important factor.

Dr. Reeves: During the last two years two members of the Radiology Department have studied this problem.[1] I think it has generally been true that a very early embolus may manifest itself by a lack of vascular markings — that is, blood flow to the lungs is cut off. Areas of congestion or atelectasis may not be noted until later, but an area of lung that has a decreased vascular supply may exhibit this finding very early. I know of a few cases that have been so diagnosed and proved.

A Physician: Would there have been any advantage in making an x-ray examination that early? Do you think one might do the patient more harm than by waiting a short time?

Dr. Adams: It might help in the early stage. But recognizing that one has the proper set-up for embolism and then carefully evaluating the history are equally, if not more, important.

Dr. Reeves: We do have a set-up whereby we can take the films with the patient in bed. One other point: Dissecting aneurysms not infrequently can be picked up on x-ray examination.

Clinical Diagnoses

Cerebrovascular accident.
Myocardial infarction.

Dr. Balboni's Diagnosis

Myocardial infarction with rupture of the heart.

Anatomical Diagnoses

Coronary thrombosis with myocardial infarction and rupture.

Hemopericardium with cardiac tamponade.

Myocardial infarct, old, with aneurysm formation.

Pathological Discussion

Dr. David Kahn: Dr. Balboni was quite right in his prediction that there was an acute myocardial infarction with rupture of the myocardium and cardiac tamponade. The pericardial cavity contained 300 cc. of blood and blood clot. There was a small aneurysmal dilatation of the anterior wall of the left ventricle just above the apex. In the center of this there was a break in the epicardial surface and a tract could be demonstrated running from the epicardial to the endocardial surface. There was coronary sclerosis involving all the branches; this was most severe in the anterior descending branch of the left coronary artery, which had a fairly recent thrombus occluding its lumen, 2.5 cm. from its origin. In the myocardium there were two distinct lesions. Just above the apex in the area of aneurysmal dilatation the myocardium was thin and fibrous. Superimposed on this was a second lesion, a recent myocardial infarct; this involved the whole thickness of the anterior wall of the left ventricle and almost the entire interventricular septum. Histologic examination showed lesions in the myocardium comparable to the gross findings. In the area of dilatation, the wall was very thin and consisted of dense fibrous tissue, scattered throughout which were a few myocardial fibers; this undoubtedly represented a healed myocardial infarct in which, during healing and subsequently, an aneurysmal dilatation had formed. In addition, in this area and in sections from the interventricular septum a recent myocardial infarct was present that was histologically compatible with ten days' duration. The lungs were not unduly congested.

By far the most common cause of myocardial rupture is infarction. The consensus from a large series is that rupture occurs in 8 to 9 per cent of acute myocardial infarctions. When, as is most common, the rupture occurs through the anterior or posterior wall of the left ventricle, hemopericardium and sudden death result; rarely, the rupture may occur through an infarct of the interventricular septum, in which case the patient may live for several months, usually with severe cardiac failure. Factors that cause an increase in the intraventricular pressure are associated with the highest percentage of ruptures — such as arterial hypertension and aortic stenosis. It is interesting in this respect that in a post-mortem series of acute myocardial infarcts in psychopathic patients 75 per cent of these had ruptured[2]; there was apparently no conscious perception of the pain and the patients kept on with their usual activities, thus maintaining a high intraventricular pressure. The size and extent of the infarction are also important with regard to the occurrence of rupture; through-and-through infarcts rupture much more commonly than those that do not involve the whole thickness of the myocardium, and moderate-sized infarcts rupture more commonly than either very small or very large infarcts. In respect to the latter, it is likely that with massive myocardial infarction the intraventricular pressure is low. In the present case the rupture occurred through an area of fibrosis, which is unusual because fibrous tissue, being more resistant to anoxemia than myocardial fibers, is usually believed to afford some protection against rupture. Probably in this case the circulation to the point of rupture was so impaired that the scar tissue became infarcted, as well as the myocardial fibers. Rupture may occur at any time during the first week, which is the period before organization is well established; it may occur during the second week but is rare after the third week. If it does occur after this time it is probably the result of another acute infarction.[3]

A Physician: Was there a pericarditis?

Dr. Kahn: In the presence of so much blood in the pericardial cavity it is difficult to make a statement about a pre-existent fibrinous pericarditis. There was no organizing pericarditis. The physical signs noted two days before the rupture certainly indicated some pericarditis.

Dr. Balboni: Dr. Adams, if you were caring for a patient such as this one, in whom you felt sure of a diagnosis of myocardial infarction, would you x-ray the chest on entry to the hospital?

Dr. Adams: No; I think there is something to be said for knowing what not to do.

References

1. Hanelin, F., and Eyler, W. R. Pulmonary artery thrombosis: roentgen manifestations. *Radiology* **56**:689-703, 1951.
2. Jetter, W. W., and White, P. D. Rupture of heart in patients in mental institutions. *Ann. Int. Med.* **21**:783-802, 1944.
3. Mallory, K., White, P. D., and Salcedo-Salgar, J. Speed of healing of myocardial infarction. *Am. Heart J.* **18**:647-671, 1939.

CASE 38012

Presentation of Case

A sixty-four-year-old woman entered the hospital because of inability to move her legs.

For two to three weeks before entry she had had mild "cramps" in the calves of both legs, partially relieved by massage. Three days before admission she suddenly developed paralysis and anesthesia in both legs; she fell to the floor and could not rise again. There was no loss of consciousness. From that time on, the condition of the legs remained unchanged, except that they became swollen a few hours after the onset of paralysis. A day or so later she noted a dull ache in the lower back; there was

no pain otherwise. Meanwhile, she had complete urinary retention.

For five or six years her appetite had been very poor, and she had subsisted on coffee, toast and potatoes, with an occasional hamburger; she had had no green vegetables or milk for two years. She had had periodic nonseasonal attacks of asthma for eighteen years. For two months she had noted exertional dyspnea without orthopnea.

Physical examination revealed a slightly obese, sallow, apathetic, unco-operative woman. She was oriented for time and place. The tongue was smooth and shiny. There were pigmented skin lesions on the elbows. There were crackling rales in the dependent portions of both lungs and scattered high- and low-pitched wheezes over the upper lungs anteriorly. The heart was enlarged to the left anterior axillary line, and a Grade II aortic systolic murmur was transmitted to the neck vessels. The optic fundi and the cranial nerves were normal. There was complete flaccid paralysis and areflexia of both legs. Pain and light touch sensations were absent bilaterally up to the knees anteriorly and to the mid-thigh and around the perineum posteriorly. There was decreased appreciation of pinprick over the anterior thighs; sensation gradually became normal as the inguinal regions were approached. Vibratory sense was diminished over both feet. Position sense was normal. Anal-sphincter tone was poor, and the bladder was distended halfway to the umbilicus. There was +++ pitting edema of the legs up to the knees.

The temperature was 102°F., the pulse 110 and the respirations 30. The blood pressure was 170 systolic, 70 diastolic.

Examination of the blood showed the white-cell count to be 8200, with 87 per cent neutrophils, the hemoglobin 5.5 gm., the red-cell count 3,600,000, the hematocrit 23 and the mean corpuscular volume 64 cubic microns. A blood smear showed marked microcytosis and hypochromia of the red cells. The total protein was 5.4 gm., with an albumin-globulin ratio of 2.9, and the nonprotein nitrogen 38 mg. per 100 cc. The urine had a specific gravity of 1.010 and gave a + reaction for albumin; the sediment was loaded with white cells. Lumbar puncture revealed normal pressures and dynamics. The spinal fluid contained 3 red cells and 1 lymphocyte per cubic mm. The total protein was 18 mg. per 100 cc. The spinal-fluid Wassermann test was negative. Gastric analysis showed the presence of free hydrochloric acid in a fasting specimen. The stools were brown and gave a negative guaiac reaction. The venous pressure and circulation time were normal. Electrocardiogram showed a normal sinus rhythm at a rate of 100. The PR interval was 0.18 second and the QRS interval 0.07 second; the voltage and axis were normal. The ST segment sagged in Leads 1, 2, AVF, V_5 and V_6. The T waves were flat in Leads 3 and AVL and diphasic in Leads 1, 2 and AVF. A roentgenogram of the chest showed the heart to be enlarged, particularly in the region of the left ventricle. There was fluid in the left pleural cavity, extending up to the level of the eighth rib in the posterior axillary line. The lower-thoracic and upper-lumbar vertebras were minimally mottled in appearance, with some haziness of the cortical margins.

The patient received intravenous thiamine and digitalis without improvement of symptoms. The temperature remained elevated between 100 and 102°F. On the eighth day the patient had an attack of pain in the epigastrium that radiated into the left upper anterior chest and was followed by marked dyspnea. Examination showed the heart and lungs to be unchanged. The pulse was 128 and regular; the blood pressure was 160 systolic, 80 diastolic. After ten to fifteen minutes the pain and dyspnea gradually disappeared. The patient died on the following day during a similar attack.

Differential Diagnosis

Dr. Ruth Stauffer*: Certainly the reason for this patient's first admission to the hospital was the development of a neurologic disorder. The history indicates a dramatic onset, with sudden development of a paraplegia that presumably remained unaltered for the nine days of the last illness. First I shall attempt to localize the neurologic lesion. A symmetrical, complete, flaccid paralysis of both lower limbs was described. Tendon reflexes were absent at both knees and ankles; absence of these reflexes, mediated solely through a spinal arc, points to some interruption or disturbance of one of the components of this arc. The neurologic signs further indicate that this was probably located in the spinal cord — the second, third and fourth lumbar cord segments being spinal centers for the knee jerks, the fifth lumbar and first sacral segments for the ankle jerks, and the fifth lumbar and the first and second sacral segments for the superficial plantar reflex.

The sensory disturbance involved primarily the modalities of pain and light touch. Vibratory sensibility was diminished distally and postural sensibility was apparently completely preserved. The protocol does not mention temperature perception. This distribution of sensory loss does not fit into that of peripheral nerve distribution but is rather segmental, with a significant pattern implicating the fourth and fifth lumbar and the five sacral dermatomes with shading of sensory loss over the first, second and third lumbar dermatomes. Once the sensory disorder is located, a question arises about the preservation of the postural sensibility and relative preservation of the perception of vibration. If touch had been partially preserved there would be no question that the posterior funiculi of the cord had escaped; therefore, I think one can only say

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that there was relative sparing of the posterior columns. In addition, the disturbance of the bladder and the anal sphincter aid in locating the lesion in the spinal cord. The anatomic diagnosis, therefore, is a spinal-cord lesion, the equivalent of a partial transection with relative sparing of the posterior funiculi. The only other questionable neurologic abnormality would be that of the patient's behavior — her lack of co-operation and the possible sensorial defect. However, it was stated that she was fully oriented. Therefore, I think the principal lesion was in the spinal cord below the level of the second lumbar segment, and one cannot be sure whether a spinal-shock phenomenon really existed here or whether the findings are indicative of the longitudinal extent of the lesion.

What are the conditions that would cause the clinical picture of an acute transverse lesion of the cord? Three of them — multiple sclerosis, acute infectious myelitis and spontaneous hematomyelia — can be dispensed with rather quickly. Among others to be considered in more detail is extradural compression, one of the causes of which is spinal epidural infection or abscess. In this patient no locus of infection was found. Such an infection might cause pain referred to the vertebral column, with paraplegia, anesthesia and vesical and rectal disturbances. Epidural carcinomatous metastases or granuloma may also present a similar picture and may be of rapid rather than sudden onset — "rapid" meaning over a twenty-four-hour period, rather than "sudden," in the sense that this was.

The next diagnosis to be considered is that of thrombosis of the anterior spinal artery and its collaterals. This is usually related to endarteritis of spinal vascular syphilis or tuberculosis and rarely occurs with other vascular diseases, with acute pyogenic meningitis or after intrathecal injection. Syphilis is excluded by the cerebrospinal-fluid findings. I can see no positive reason to suspect tuberculosis. Meningitis was not present. Occlusion of the anterior spinal artery may occur from extradural masses — by epidural abscess, carcinoma or granuloma causing pressure on the vessel. A finding of a dynamic block by lumbar puncture, abnormalities of the vertebras in the x-ray films and pain and tenderness at the site of the affected vertebras should assist in determining whether or not pressure exists.

May we see the x-ray films, Dr. Wyman?

Dr. Stanley M. Wyman: The chest films were taken with the patient lying on her back; this magnifies the left-ventricular contour, but I think the left ventricle is enlarged and the aorta is definitely calcified and tortuous. There is a small amount of fluid in the left pleural space. The lung fields are otherwise not remarkable. The films we have of the spine are limited to the lower-thoracic and upper-lumbar regions. The canal seems to be normal in contour; there is no obvious erosion of the vertebral bodies. The pedicles appear to be preserved. There is some arteriosclerosis of the abdominal aorta. I am not too impressed by the bony changes described in the protocol; they are certainly minimal.

Dr. Stauffer: Would you comment on the width of the thoracic aorta?

Dr. Wyman: As nearly as I can determine from these films, it is normal. I can see some portions of the opposing walls of the aorta in the lumbar regions; it seems to be within normal limits there also. I do not see any evidence of an aneurysm.

Dr. Stauffer: At this point I shall discuss the associated clinical features in order to establish the cause of the neurologic disorder or alternatively to rule out the relation of these features to the neurologic disorder. The legs were edematous. I was wondering whether the femoral and popliteal pulses were normal. Also, what were the color and temperature of the lower limbs?

Dr. Lawrence J. Barrows: Both posterior-tibial and both dorsalis-pedis pulses were felt. The edema was said to have arisen in one to two days; the legs were white and not cold.

Dr. Stauffer: The question of the cause of the edema then comes up. I doubt that it could have been due to occlusion of the pelvic veins. The only explanation that I would have for it at present is that the edema was due either to the nutritional deficiency, which I shall comment on in a moment, or to deep thrombosis due to the loss of normal tone and voluntary muscular contraction in the lower limbs following paralysis.

The next condition to be considered is the cardiovascular status. The heart was enlarged; there was some hypertrophy and questionably some dilatation in relation to the anemia that this patient had. The aortic systolic murmur is also to be considered. On the basis of the data presented I doubt that I could make a diagnosis of aortic stenosis in a woman of that age. The murmur here may well have been related to the anemia. The electrocardiogram, I am told, shows minimal changes consistent with the left-ventricular hypertrophy and at most represents strain. The normal circulation time and venous pressure are against the possibility of chronic passive congestion, which could explain the pleural effusion, the basal rales and the edema of the lower extremities.

The anemia was severe — 5.5 gm. of hemoglobin. The blood picture indicated a microcytic hypochromic anemia; I certainly think that the murmur, the cardiac enlargement and the dyspnea may possibly have been explained on this basis if the anemia had been prolonged. What about the origin of the anemia? The possibility of nutritional defect is good. I have been wondering, not being a hematologist, if a nutritional anemia ever reaches a 5.5-gm. level. I am told that it might. I would suspect, however, that something else was involved — either bleeding or malignant disease.

Would someone like to comment on the anemia in this patient?

DR. MARIAN W. ROPES: It would be surprisingly low for a nutritional anemia.

DR. STAUFFER: The fever might be associated with either the anemia, infection of the bladder following paralysis, or malignancy. I think I would like to dispense with the urinary findings by explaining them as secondary to the neurologic disorder. This brings me to the patient's nutritional state. The diet described is certainly likely to result in deficiency, which the patient reflected in some aspects. The blood protein was only slightly lowered, but the albumin-globulin ratio was normal. If any vitamins were represented in the diet they were thiamine and, perhaps, niacin and riboflavin. However, the skin lesions of the elbow are in keeping with a niacin deficiency, and it is quite easy, in glancing over the total clinical history and findings, to wonder about a thiamine deficiency as an explanation for the whole syndrome. Of interest is the fact that to my knowledge sudden paralysis has not occurred in any of the cases of vitamin B deficiency reported in the literature.

In a woman of this age I have to think of cancer in relation to the pleural effusion. Without further evidence I cannot make a positive statement, so I shall leave it as a serous effusion, of questionable origin. With no definite indication of cancer, although there is much to lead me to suspect it, — the blood picture, the fever and the as yet unexplained pleural effusion, — I feel obliged to omit secondary neoplasm as the cause of the spinal-cord disorder.

What remains is a primary thrombosis of the anterior spinal artery or a dissecting aneurysm. A dissecting aneurysm may cause ischemic necrosis of the spinal cord by occluding or shearing off the intercostal or lumbar arteries and secondarily by occluding the blood supply via the anterior spinal artery to the cord. The end branches of these spinal arteries are terminal; therefore occlusion of an end branch is followed by softening. The clinical history is not consistent with the classical picture of dissecting aneurysm. There was no pain at the beginning when the neurologic signs occurred. The duration, although not completely against this, indicates that it was a long history; the average time of survival is much less. No shock was described at the onset of the neurologic disorder. Both the episode of dyspnea on the day prior to death, with no particular changes in clinical signs, and the final episode could have been due to pulmonary infarcts, to coronary occlusion or to dissecting aneurysm. It is difficult, without further data, to say which of these it was. Certainly the x-ray finding of calcification of the thoracic and abdominal aorta is of interest. Although hypertensive cardiovascular disease cannot definitely be diagnosed from the data available, certainly she had an elevated blood pressure with wide pulse pressure, perhaps precipitated by the anemia. The possibility of dissecting aneurysm still remains, but this diagnosis cannot be made on the basis of the clinical history as presented.

I therefore believe that this patient had a myelomalacia of the lumbosacral segments due to anterior-spinal-artery thrombosis relatively sparing the posterior funiculi, that she had multiple nutritional deficiencies, — specifically of vitamins, — and that she probably died of pulmonary infarction.

DR. BENJAMIN CASTLEMAN: Dr. Ayer, have you any comments?

DR. JAMES B. AYER: Only that the main arterial supply to that region is the arteria radicularis anterior magna of Adamkiewicz — a very large artery at about the second lumbar segment, which was the level of that lesion. I think that a thrombosis of that artery at any point in its course could produce this picture.

DR. JAMES C. WHITE: How severe was the pain? Was it the intense pain that accompanies dissecting aneurysm of the aorta?

DR. BARROWS: She had no chest pain on admission. It was not the severe chest pain that is described in situations of that sort. There was a relatively silent onset. The patient was well until paralyzed. The only time she complained of pain was during the final episode on the ward.

DR. WHITE: How severe was that?

DR. BARROWS: It was quite severe. It followed a drink of cold water, and the patient thought that the cold water caused it.

DR. WHITE: I am interested in the possibility of dissecting aneurysm. However, they usually rupture in the chest and the pain is more thoracic; it would be unusual to find it fairly low.

DR. BARROWS: The paralysis occurred eight days before the final episode of pain.

CLINICAL DIAGNOSES

Anterior spinal artery thrombosis.
Bronchopneumonia.
Arteriosclerotic heart disease.
Myocardial infarction.
Malnutrition.

DR. STAUFFER'S DIAGNOSES

Thrombosis of anterior spinal artery, with myelomalacia of lumbosacral segments.
Pulmonary infarction.
Multiple nutritional deficiencies.

Anatomical Diagnoses

Anterior spinal artery thrombosis, recent.
Spinal cord infarcts, multiple.
Pulmonary emboli, extensive, bilateral.
Pulmonary infarct, right lower lobe.
Cerebral atherosclerosis, severe.
Cerebral infarcts, healed, multiple, of basal ganglia, internal capsule and pons.

Pathological Discussion

Dr. Castleman: The autopsy showed that the severe pain that the patient had before death was due to a pulmonary infarction, as Dr. Stauffer predicted. The right lower lobe was very much infarcted, and there were emboli in other branches of the pulmonary artery. The heart showed left-ventricular hypertrophy such as you would expect with mild hypertension, and the kidneys showed a mild degree of nephrosclerosis. Aside from arteriosclerosis in all the other organs, we found nothing else in the rest of the body. The brain and spinal cord will be described by Dr. Richardson.

Dr. Edward P. Richardson, Jr.: As Dr. Stauffer predicted, there was a thrombus in the anterior spinal artery at the lumbosacral level. In the sections, the thrombus could not be traced higher than approximately the first lumbar segment. Grossly there was extensive softening of the anterior portion, — the anterior white funiculi and the gray matter of the anterior horns, — of the coccygeal and lumbar cord, extending upward into the thoracic cord to the tenth thoracic segment and perhaps to the ninth. The eighth thoracic segment was apparently intact, and the cord was normal above that level. There was evidence of vascular disease in the brain also. The cerebral arteries were severely atherosclerotic down to quite small branches, and in the basal ganglia on both sides were small scarred lesions consistent with old healed infarctions.

Microscopically, there was severe necrosis in the grossly softened portions of the cord, within which microglial phagocytes had already appeared. This destruction mainly affected the anterior part of the cord, as already stated. The posterior white columns (including the lateral pyramidal tracts) and the posterior horns of the gray matter were intact. Despite the presence of the thrombosis in the anterior spinal artery, the artery itself did not appear diseased in the available slides.

Dr. Raymond D. Adams: I wonder if we have the whole story? The anterior spinal artery does not show arteritis or atherosclerosis. I am rather intrigued by Dr. Ayer's suggestion that the process began outside the spinal canal. Some months ago we observed a case in which a syndrome just like this, with the finding of myelomalacia at autopsy, was traced to a thrombus at the origin of the tenth left intercostal artery, almost within the wall of the aorta. As a rule two or three of these branches are the main source of blood supply to the lumbosacral and lower-thoracic cord segments. If one of these vessels, which are frequently involved by atherosclerosis, becomes thrombosed, extensive infarction of the spinal cord may result. It is difficult to carry out an adequate post-mortem examination of the extravertebral arterial or venous vascular system, and in the case presented here the prosector was not allowed sufficient time to attempt such a dissection.

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ANOTHER YEAR OF DECISION

With this issue of the *Journal*, its two hundred and forty-sixth volume since the *Boston Medical and Surgical Journal* started on its long career is ushered into a world that is probably only slightly startled by the event. It may be, nevertheless, a matter of moderate interest and of some satisfaction to the local medical world, which has watched similar events take place for a considerable period of time. For this happy occasion marks also the completion of a hundred and forty years of uninterrupted service since the first number of the *New England Journal of Medicine and Surgery* made its appearance on the scene. It gets to be a habit, and habit is strong in old New England.

The year 1952 will go down in the record as a year of decision. This is a fact of importance, the significance of which is diminished only a little by its applicability, to a greater or lesser degree, to almost any year that has crashed the calendar since the world was shaken out of its post-Victorian doldrums in 1914.

There have been relatively placid periods in the world's history, but they have occurred, usually, when the shadow of some empire lay across the land and sea. Such was the peace imposed by Rome, and such was the *Pax Britannica*, which came to its close almost within a generation. Such periods of peace and prosperity, however, favored mainly the conquerors — and mainly the favored classes of the dominant nation.

Perhaps the present years of decision will result in a Peace of the United Nations, based on universal justice and with benefits that will reach all classes of society.

THE SUPPORT OF MEDICAL EDUCATION

The present status of medical education and the schools that dispense it is somewhat reminiscent of Aesop's unhappy frogs, who, discontented with the do-nothing tactics of King Log, called on Zeus for a new, more aggressive leadership to give them the help that they believed they required in discharging their amphibian functions. Zeus nodded, it will be recalled, and sent King Stork, who, after a certain amount of regimentation, gobbled up his charges as often as his stomach became empty, which was very often indeed.

There is actually nothing about the predicament of a puddleful of Grecian frogs that need necessarily remind one of the possible dangers inherent in too much federal aid, yet a great many interested parties are coming to the conclusion that God gives the greatest amount of effective help to those who also help themselves. It is on this theory that educators, among others, have been instrumental in developing the National Fund for Medical Education, Incorporated, and that graduates in medicine have helped to initiate the American Medical Education Foundation of the American Medical Association — two hearts, it may be added, that beat approximately as one.

In other types of school than those of medicine, the alumni have traditionally been called on for

aid and have been expected to make their contribution. A sound precedent is being followed by extending this custom to the medical schools, and it is apparently one that will work, for the Jefferson Medical College fund has for three years brought in contributions that now total more than $100,000 annually. This enables the school at least to maintain its teaching program, if not to increase its activities or expand its facilities. If the medical profession is on trial in this matter, it is making a very good defense for itself, at least at Jefferson.

Not all schools, of course, are equally badly off; even if the present state of insolvency is common to nearly all, they are not all involved to the same degree. The state-owned schools are generally better off than the private schools, and the large endowed universities have been better able to "cushion" their medical schools than have the less prosperous ones. How long this can continue is a matter of conjecture; few of them can probably carry on for more than another five years without relief. Obviously those schools that can be kept going only through depletion of the universities of which they are a part must before long be dropped by the wayside.

The only possible course of action now open to the medical profession, — anxious in behalf of its alma maters, — is to get solidly behind the voluntary plans for relief, carrying as much of the annual load as can be shouldered, hoping to delay as long as possible any eventual resort to federal aid, and then to keep it always at a minimum. Only in this way can governmental encroachment on the freedom of education be avoided.

Incidentally, schools that already have their own plans for raising funds from alumni do not interfere in any way with the objectives of the American Medical Association, which are simply to raise as much money as possible, for the support of medical education, from as many physicians as possible.

Certainly the problem of paying the bill for medical education will not be solved by depositing new schools, like cuckoos' eggs, in areas that can hardly support what they already have — unless the chance is openly taken that the impostors may push out of the nest those that might seem to have a prior claim to its protection.

NEWSHAWKS GATHER

Following hard, but not too hard, on the international assembly of medical editors in Stockholm in September, the editors of the thirty-three state medical journals that are nourished at the breast of the State Journal Advertising Bureau of the American Medical Association met in Chicago in November to discuss their mutual problems. It was the renewal of an old custom, after the lapse of two years, to gather together and derive what comfort there is, if any, in learning that others are encompassed by the same difficulties that beset one's own path.

It would be tedious to enumerate the speakers and the subjects that occupied two full days of conference; certain ones, however, stand out as of special interest and value.

The opening paper, for example, by Walter Kahoe, director of the medical department of J. B. Lippincott Company, outlined the many details of the job of the editor, in relation particularly to the stimulation of reader interest, — without which any publication is lost, — the balance of journal content and the function of editorials. Harry L. Shaw, general editor of Harper and Brothers, discussed the literary aspects of medical journals, stressing the necessity of condensation of material and the elimination of long as well as of unnecessary words. Would that the average prolix medical writer would take this thought to heart and measure his words like a native Lacedaemonian! There is, Mr. Shaw maintained, no such thing as good writing, but only good rewriting, another maxim to be pinned to the lampshades of all would-be authors. The speaker further referred to the increased use of *visual technics* in the transmittal of ideas, which, in publishing, implies more and better illustrations and clearer and simpler diagrams.

Lester L. Hawkes, associate professor of journalism at the University of Wisconsin, gave a painstaking analysis of the mechanical side of publishing, — the format and typography of the journals, — reminding their editors that there are now more readers who wear glasses than ever before.

The growth of the State Journal Advertising Bureau, which obtains the bulk of the national ad-

vertising for the group, was described by Alfred J. Jackson, director of the Bureau. Established by the American Medical Association in 1913 to procure advertising contracts that conformed to the rules elaborated by the Council on Drugs and Chemistry, its enrollment has increased from 22 to 33 journals and its net sales tenfold since the early twenties — to well over $600,000 in 1951.

At the final session William A. Richardson, editor of *Medical Economics*, made a valuable contribution on the type, scope and procurement of articles on the social and economic aspects of medicine. Dr. Roger I. Lee, of Boston, former president of both the American Medical Association and the Massachusetts Medical Society and dean of the profession's younger elder statesmen, brought the program to an appropriate close with a reminiscent and philosophical paper on "Medical Writing As Observed By a Reader."

PESTICIDES

The last report of the Committee on Pesticides appointed two years ago by the American Medical Association discloses a significant expansion of its educational and investigative phases. Several committee bulletins have received wide circulation, even having been translated into Spanish. With the passage of the Federal Insecticide, Fungicide and Rodenticide Act, packages of economic poisons are required in interstate commerce to carry the names of ingredients. This will make it possible for death certificates to contain more accurate data about the actual causes of death in the cases of persons dying from such poisons. The committee has made a strong plea that medical examiners and other physicians furnish more factual death certificates so that more useful data on such deaths may be obtained for tabulation and a true picture of the attendant hazards furnished to the medical profession and the public. Their inquiry service has been enlarged, and much useful information has been disseminated to various organizations.

In its investigations the committee has continued its development of safety standards for the use of pesticides, its evaluation of remedial measures and its collection and analysis of reports of poisoning by pesticides. One of its specific plans is to evaluate a possible new antidote for parathion, which is widely used in agriculture.

With the standardization of nomenclature in this field that the committee is undertaking, and with the full development of a poison-reporting system, the committee becomes a well established center to which physicians and others may direct inquiries concerning the effects of pesticides and the remedies for the various agents used for such purposes.

The New York Dental Recorder *don't think much of Dr. Allen's enamelled plates and artificial gums. It says that the remains of a set of teeth for the upper jaw, worn by the late Aaron Burr, made in France, were of precisely the same kind, and therefore there is nothing new under the sun in that line.*

Boston M. & S. J., *January 7, 1852*

MASSACHUSETTS MEDICAL SOCIETY

DEATHS

BRICKETT — Beatrice H. Brickett, M.D., of Taunton, died on December 11.

Dr. Brickett received her degree from the Woman's Medical College of Pennsylvania in 1898. She was a fellow of the American Medical Association.

A niece survives.

GILLIS — John E. Gillis, M.D., of Somerville, died on December 15. He was in his seventy-third year.

Dr. Gillis received his degree from the McGill University Faculty of Medicine in 1904.

LANCASTER — Walter B. Lancaster, M.D., of Boston, died on December 9. He was in his eighty-ninth year.

Dr. Lancaster received his degree from Harvard Medical School in 1889. He was a fellow of the American Medical Association and a past president of the American Ophthalmic Society.

A daughter and two sisters survive.

LOOK — Percy J. Look, M.D., of Andover, died on December 9. He was in his sixty-eighth year.

Dr. Look received his degree from Harvard Medical School in 1912. He was a member of the New England Pediatric Association, a fellow of the American Medical Association and a former president of the Essex North District Medical Society.

A daughter, two sons and three grandchildren survive.

RYDER — Delano R. Ryder, M.D., of Fall River, died on December 19. He was in his eightieth year.

Dr. Ryder received his degree from the University of Vermont College of Medicine in 1904. He was a fellow of the American Medical Association.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

COMMUNICABLE DISEASES IN MASSACHUSETTS FOR NOVEMBER, 1951

RÉSUMÉ

DISEASE	NOVEMBER 1951	NOVEMBER 1950	SEVEN-YEAR MEDIAN
Chancroid	1	2	2
Chicken pox	658	862	862
Diphtheria	6	9	20
Dog bite	662	849	664
Dysentery, bacillary	1	5	8
German measles	96	83	59
Gonorrhea	179	189	262
Granuloma inguinale	0	0	0
Lymphogranuloma venereum	0	1	1
Malaria	131	0	5
Measles	861	157	353
Meningitis, meningococcal	11	3	4
Meningitis, Pfeiffer-bacillus	1	4	5
Meningitis, pneumococcal	3	1	3
Meningitis, staphylococcal	0	0	0
Meningitis, streptococcal	0	0	0
Meningitis, undetermined	6	3	3
Mumps	1061	588	523
Poliomyelitis	13	56	46
Salmonellosis	11	2	4
Scarlet fever	141	290	304
Syphilis	186	129	235
Tuberculosis, pulmonary	171	196	217
Tuberculosis, other forms	8	10	10
Typhoid fever	2	2	2
Undulant fever	0	2	3
Whooping cough	297	445	539

COMMENT

The diseases notably above the seven-year median for November are German measles, malaria, measles, meningococcal meningitis, mumps and salmonellosis. The malaria cases were reported from military hospitals and represent relapses in men returning from Korea and other foreign areas.

Diseases below the seven-year median for this month are chicken pox, diphtheria, poliomyelitis, scarlet fever and whooping cough.

The 96 cases of German measles represent the third highest figure reported for the month of November since 1917.

The 1061 cases of mumps are the largest number on record for this month. This number is more than twice that of the seven-year median for this disease.

Six cases of diphtheria are the second lowest number ever recorded in Massachusetts during November.

GEOGRAPHICAL DISTRIBUTION OF CERTAIN DISEASES

Diphtheria was reported from: Boston, 2; Cambridge, 1; Lowell, 1; New Bedford, 2; total, 6.

Dysentery, bacillary, was reported from: Wellesley, 1.

Encephalitis, infectious, was reported from: Worcester, 1.

Hepatitis, infectious, was reported from: Camp Edwards, 20; Greenfield, 1; Haverhill, 1; Wrentham, 1; total, 23.

Choriomeningitis, lymphocytic, was reported from: Plymouth, 1; Weston, 1; total, 2.

Malaria was reported from: Camp Edwards, 127; Fort Devens, 4; total 131.

Meningitis, meningococcal, was reported from: Boston, 1; Framingham, 1; Leominster, 1; Lynn, 1; Medford, 1; Milford, 1; Seekonk, 1; Upton, 1; Walpole, 1; Weymouth, 1; Worcester, 1; total, 11.

Meningitis, Pfeiffer-bacillus, was reported from: Wellesley, 1.

Meningitis, pneumococcal, was reported from: Malden, 1; Quincy, 1; Worcester, 1; total, 3.

Meningitis, undetermined, was reported from: Barnstable, 1; Boxford, 1; Cambridge, 1; Fall River, 1; Northampton, 1; Stoughton, 1; total, 6.

Poliomyelitis was reported from: Arlington, 1; Ashland, 1; Camp Edwards, 1; Dover, 1; Lynn, 1; Malden, 2; Newton, 1; Revere, 1; Shirley, 1; Spencer, 1; Walpole, 1; Worcester, 1; total, 13.

Salmonellosis was reported from: Boston, 2; Cambridge, 1; Dartmouth, 1; Dedham, 1; Ipswich, 2; Milton, 1; New Bedford, 1; Springfield, 1; Worcester, 1; total, 11.

Septic sore throat was reported from: Boston, 1; Fall River, 1; Methuen, 1; total, 3.

Tetanus was reported from: Holyoke, 1.

Trichinosis was reported from: Auburn, 1; Camp Edwards, 1; Falmouth, 1; Fitchburg, 1; total, 4.

Typhoid fever was reported from: Cambridge, 1; Springfield, 1; total, 2.

NONCLINICAL NOTES

Dr. C. Guy Lane, of Boston, has been elected president of the American Academy of Dermatology and Syphilology.

Dr. Lane, who is professor emeritus of clinical dermatology at Harvard Medical School, is a member of the editorial board of the *New England Journal of Medicine.*

Dr. William L. Holt, of Wellesley Hills, has accepted an appointment as professor and director of the Department of Psychiatry of Albany Medical College and psychiatrist-in-chief at the Albany Hospital.

Dr. Chester S. Keefer was recently honored at a dinner given by his past and present associates in recognition of his tenth year as Wade Professor of Medicine at Boston University School of Medicine and physician-in-chief and director of the Evans Memorial at the Massachusetts Memorial Hospitals.

Tribute was paid to Dr. Keefer for his many accomplishments during this period. The dinner was the occasion for a presentation to the hospital of an oil painting of Dr. Keefer.

CORRESPONDENCE

INHALATION OF ALCOHOL

To the Editor: An article recently published in the November 29 issue of the *Journal* has aroused my interest. I refer to the article entitled "Inhalation of Ethyl Alcohol for Pulmonary Edema," by Drs. Gootnick, Lipson and Turbin.

Inhalation of alcohol vapor for pulmonary edema was studied in animals in my laboratory three years ago. Although the statement that "no clinical experience with this agent has as yet appeared in the literature" is literally true, several reports dealing with clinical studies performed at the Mt. Sinai Hospital of Chicago and the Cook County Hospital by myself and co-workers have been publicly presented. I am referring to a paper reporting on 10 cases of pulmonary edema that was read at the June meeting of the American Heart Association; an exhibit on 34 cases presented last October at the New York Academy of Medicine; several lectures in Chicago; and an extensive correspondence with Army centers, Veterans Hospitals and 12 physicians in New York State, Illinois, Indiana, Pennsylvania and Ohio. A study reporting on 34 cases is to be published in *Circulation.* This study reports also on several methods of administration, including one by mask and one by nasal catheter, with detailed instructions. Our total number of patients is now 45, most of whom had an extremely favorable result. It is comforting to note a confirmation in the work of Gootnick and his co-workers.

I thought that your readers might be interested in hearing about this extensive study, and I shall be glad to supply further information to anyone requesting it.

ALDO A. LUISADA, M.D.

Chicago, Illinois

CONCERNING FATAL TRANSFUSION REACTION

To the Editor: The description of fatal transfusion reactions by Borden and Hall in the November 15 issue of the *Journal* is a timely reminder that those participating in the processing of blood bear a grave responsibility. The authors are to be commended for their reëmphasis on this clinical syndrome. Several nonclinical statements must be challenged, however, in the interests of hospital practice in general.

The authors state: "The mass production of uniformly sterile equipment, parenterally administered fluids and blood bottles requires accurate timing in processing methods and rigid controls *that would be impractical and are not generally available in the average hospital or blood bank laboratory.*"

I have italized the objectionable portion of the sentence. The first portion is a statement of fact too obvious to require comment. A hospital that is convinced that accurate timing in processing methods is impractical and unavailable is negligent in the care of its patients. It is this philosophy that I challenge.

Anyone versed in sterilizing practice can predict that bottles processed as described by the authors will be unsterile. This is because there are major conceptual errors in planning the processes. Evacuated, sealed bottles were exposed to steam at 121°C. in an autoclave for twenty minutes. This treatment sterilized the outside of the bottles by moist heat because the thermal death time in saturated steam is thirteen minutes at 121°C. The inside, however, remains unsterile because each sealed bottle is a miniature dry-heat oven. The thermal death time in dry heat at 121°C. is 240 minutes.

The folly of selecting telltale indicators for the control of sterilization is well illustrated.

Further, the authors perpetuate the myth that there are "cold spots" in large autoclaves. The temperature in a properly operated steam sterilizer is uniform throughout. "Cold spots" result from blundering in packaging, loading and operation of the same fundamental sort that would condone a standing postoperative nursing order for 60-mg. doses of morphine.

The facts of sterilization are readily available to all in the form of a monograph, *Aseptic Treatment of Wounds*, published in 1948 by the Macmillan Company.

Those charged with the preparation of sterile supplies in hospitals must be competent in their field. Certainly every hospital where surgery and obstetrics are performed must have both equipment and personnel to accomplish sterilization of supplies.

CARL W. WALTER, M.D.

Boston, Massachusetts

Dr. Walter's letter has been read by Dr. Borden and Dr. Hall, who offer the following reply:

To the Editor: The many contributions and recognized authority of Dr. Carl Walter in the field of sterilization practice are well known to the authors. His comments and criticisms are of considerable interest.

The blood causing the fatalities described was procured on contract from a large private blood bank located in a metropolitan area and licensed by the National Institute of Health to ship blood and its products across state lines. The bottles were processed by the bank and autoclaved with citrate solution in them, so the interior was presumably exposed to moist heat.

Regardless of the adequacy of processing methods used in the preparation of tubing and fluids for intravenous use, there is always the possibility of mechanical failure and human error. To ensure safety of the final product, tests for sterility and pyrogenicity are required of commercial firms dispensing blood bottles or fluids for parenteral use. These precautions seem to be worth while if not indispensable. Hospitals preparing blood bottles and parenteral fluids should therefore be required to use them.

CRAIG BORDEN, M.D.
WENDELL HALL, M.D.

Minneapolis, Minnesota

BOOK REVIEW

Terminal Care for Cancer Patients: A survey of the facilities and services available and needed for the terminal care of cancer patients in the Chicago area. 8°, paper, 211 pp., with 39 tables. Chicago: The Central Service for the Chronically Ill of The Institute of Medicine of Chicago, 1950. $1.25.

This survey was made possible by a grant from the American Cancer Society. It is a study of the prevalence of cancer in Cook County, Illinois, and of the facilities available for the care of the incurable terminal case, with conclusions based on the survey and recommendations for improvement in service.

There are many statistical tables dealing with sex, age, marital status and so forth, which correspond closely with the figures for the United States as a whole. Stress is laid on the necessity of close co-operation of the social and financial agencies that may be called on to aid the impecunious family. In approximately 50 per cent of cases no financial aid was necessary. Twenty-five per cent could assume a portion of the expense, and twenty-five per cent were entirely dependent on charity.

The number of cases requiring care in a general hospital, hospital for chronic disease, public or private nursing home or at home is discussed, with consideration of the relative costs. The need of a larger number of practical nurses is stressed and special emphasis is laid on the necessity of maintaining the morale of the patient and family.

The publication is somewhat long, — about 200 pages,— but will be of great value to a community planning a well integrated program for the care of incurable cases of malignant disease.

CHANNING C. SIMMONS, M.D.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

The Differentiation of Escherichia and Klebsiella Types. By F. Kauffmann, M.D., chief, International Salmonella Center, State Serum Institute, Copenhagen, Denmark. 8°, cloth, 57 pp., with 9 tables. Springfield, Illinois: Charles C Thomas, 1951. $2.00. (Publication Number 84, American Lecture Series.)

Introduction to a Psychoanalytic Psychiatry. By Paul Schilder, M.D., Ph.D. Authorized translation by Bernard Glueck, M.D. Second printing. 8°, cloth, 178 pp. New York: International Universities Press, Incorporated, 1951. $3.25.

Brain and Personality: Studies in the psychological aspects of cerebral neuropathology and the neuropsychiatric aspects of the motility of schizophrenics. By Paul Schilder, M. D., Ph.D. 8°, cloth, 136 pp. New York: International Universities Press, Incorporated, 1951. $2.50.

Physiology of Heart and Circulation and Its Clinical Application in Physical Medicine. A symposium presented at the twenty-seventh annual conference of the American Physical Therapy Association, Cleveland, Ohio, June 26-30, 1950. 4°, paper, 63 pp. New York: American Physical Therapy Association, 1951. $1.00.

Symbolic Realization: A new method of psychotherapy applied to a case of schizophrenia. By M. A. Sechehaye. 8°, cloth, 184 pp., with illustrations. New York: International Universities Press, Incorporated, 1951. $3.25. (Monograph Series on Schizophrenia No. 2.)

Alcoholism and Social Stability: A study of occupational integration in 2,023 male clinic patients. By Robert Straus, Ph.D., assistant professor of sociology, Yale Center of Alcohol Studies, and Selden D. Bacon, Ph.D., director, Yale Center of Alcohol Studies, and associate professor of sociology, Yale University. 8°, paper, 30 pp., with 24 tables. New Haven, Hillhouse Press, 1951. (Published for the Yale Center of Alcohol Studies.)

Hope and Help for the Alcoholic. By Harold W. Lovell, M.D. 12°, cloth, 215 pp. New York: Doubleday and Company, Incorporated, 1951. $2.75.

The Control of Cross Infection in Hospitals. By The Cross Infection in Hospitals Committee of the Medical Research Council. 8°, paper, 49 pp., with 6 illustrations. London: His Majesty's Stationery Office, 1951. 1s. 9d. net. Privy Council. Medical Research Council. Memorandum No. 11. (Revised edition, 1951.)

Psychiatric Aspects of Juvenile Delinquency: A study prepared on behalf of the World Health Organization as a contribution to the United States programme for the prevention of crime and treatment of offenders. By Lucien Bovet, M.D., consultant in mental health, World Health Organization, and médecin-chef de l'Office médico-pédagogique attaché au Département de Justice et Police de l'État de Vaud, Lausanne, Switzerland. 8°, paper, 90 pp. Geneva: World Health Organization, 1951.

Report on the Malaria Conference in Equatorial Africa: Held under the joint auspices of the World Health Organization and of the Commission for Technical Co-operation in Africa South of the Sahara, Kampala, Uganda, November 27–December 9, 1950. 8°, paper, 72 pp. Geneva, Switzerland: World Health Organization, 1951. 3s 6d, $0.45. World Health Organization Technical Report Series No. 38.

Medicine of the Year. Editorial direction, John B. Youmans, M.D., dean, School of Medicine, Vanderbilt University. Third issue, 1951. 8°, cloth, 298 pp. Philadelphia: J. B. Lippincott Company, 1951. $5.00.

The Social Consequences of Pneumoconiosis Among Coalminers in South Wales. By P. Hugh-Jones and C. M. Fletcher. 8°, paper, 54 pp., with 4 illustrations and 16 tables. London: His Majesty's Stationery Office, 1951. 1s. 9d. net. (Privy Council, Medical Research Council Memorandum No. 25.)

Studies From the Rockefeller Institute for Medical Research. (Reprints.) Volume 141. 8°, cloth, 563 pp., with illustrations and tables. New York: The Rockefeller Institute for Medical Research, 1951.

Transactions of the American Association of Genito-Urinary Surgeons (Sixty-first annual meeting held at Hershey, Pennsylvania, May 24–26, 1950). Volume XLII. 8°, cloth, 211 pp., with illustrations and tables. Baltimore: Williams and Wilkins Company, 1951.

Diseases of the Heart and Circulation. By Paul Wood, O.B.E., M.D. (Melbourne), and F.R.C.P. (London), director, Institute of Cardiology, London, physician, National Heart Hospital, physician in charge of the Cardiac Department, Brompton Hospital, and cardiologist, Rheumatic Fever Unit, Canadian Red Cross Memorial Hospital, Taplow. 8°, cloth, 589 pp., with illustrations. Philadelphia: J. B. Lippincott Company, 1951. $12.50.

Scoliosis: Pathology, etiology, and treatment. By Samuel Kleinberg, M.D., attending orthopedic surgeon, Hospital for Joint Diseases, consulting orthopedic surgeon, Lebanon Hospital, Maimonides Hospital and Hospital for Special Surgery, New York City, and lecturer in orthopedics, New York University Medical School. 8°, cloth, 286 pp., with 163 illustrations. Baltimore: The Williams and Wilkins Company, 1951. $7.50.

Functional Anatomy of the Limbs and Back: A text for students of physical therapy and others interested in the locomotor apparatus. By W. Henry Hollinshead, M.S., Ph.D., head of the Section on Anatomy, Mayo Clinic, Rochester, and professor of anatomy, Mayo Foundation, University of Minnesota. 8°, cloth, 341 pp., with 122 illustrations. Philadelphia: W. B. Saunders Company, 1951. $6.00.

Reality and Dream: Psychotherapy of a Plains Indian. By George Devereux, Ph.D., staff ethnologist, Winter Veterans Administration Hospital, and lecturer, Topeka Institute for Psychoanalysis. With prefaces by Karl A. Menninger, M.D., and Robert H. Lowie, Ph.D., and psychological tests edited and interpreted by Robert R. Holt, Ph.D. 8°, cloth, 438 pp., with 13 illustrations and 12 plates. New York: International Universities Press, 1951. $7.50.

Large Scale Rorschach Techniques: A manual for the group Rorschach and multiple choice tests. By M. R. Harrower, Ph.D., research and consulting psychologist, New York City, and M. E. Steiner, M.A., research psychologist, General Electric Company, Bridgeport, Connecticut. With contributions by Floyd O. Due, M.D., assistant clinical professor of psychiatry, University of California Medical School, Beatrice A. Wright, Ph.D., assistant professor of psychology, San Francisco State College, and M. Erik Wright, Ph.D., M.D., professor of clinical psychology, University of Kansas Medical School and University of Kansas. Second edition. 8°, cloth, 353 pp., with 136 illustrations and 87 tables. Springfield, Illinois: Charles C Thomas, 1951. $8.50. (Publication Number 82, American Lecture Series.)

NOTICES

SPRINGFIELD ACADEMY OF MEDICINE

Dr. Frank Lahey, of the Lahey Clinic, Boston, will speak at a meeting of the Springfield Academy of Medicine on January 8. His subject will be "Lesions of the Large Intestines: Their Diagnosis and Management."

HARVARD MEDICAL SOCIETY

The Harvard Medical Society will hold a meeting on Tuesday, January 15, at 8:00 p.m., in the auditorium of Beth Israel Hospital. A program will be presented by the Department of Surgery of the hospital. Dr. Jacob Fine will preside.

PROGRAM

Effect of Hemisulfur Mustard on the Ascites of Intraperitoneal Carcinoma. Dr. Arnold M. Seligman.

Criteria for Suitability of Plasma Volume Expanders. Evaluation of Polyvinylpyrrolidone. Dr. Herbert A. Ravin.

Role of Intestinal Flora in Experimental Vascular Injuries to the Gut. Dr. Jacob Fine.

The Bacterial Factor in Hemorrhagic Shock: Standard Control Experiment. Dr. Howard A. Frank.

Effect of Antibiotics on Irreversibility to Transfusion. Dr. Jacob Fine.

GREATER BOSTON MEDICAL SOCIETY

The next meeting of the Greater Boston Medical Society will be held on Wednesday, January 16, at 8:30 p.m., in the auditorium of Beth Israel Hospital.

Drs. William E. Browne, Dean A. Clark, David Halbersleben and Reginald H. Smithwick will present a panel discussion of "Social-Economic Trends in Medicine."

SOCIETY MEETINGS AND CONFERENCES

JANUARY 4. New England Deaconess Hospital Clinic. Page 548, issue of October 4.

JANUARY 5–30. Springfield Hospital. Page 1032, issue of December 27.

JANUARY 5, FEBRUARY 2, MARCH 1, APRIL 5 AND MAY 3. New England Society of Anesthesiologists. Post-Graduate Education Course. Page 966, issue of December 20.

JANUARY 7. New England Cardiovascular Society. Page 1032, issue of December 27.

JANUARY 7, 11, 21 and 28. Anesthesia Teaching Conferences. Page 1031, issue of December 27.

JANUARY 7, FEBRUARY 25 AND APRIL 15. Massachusetts Society for Research in Psychiatry. Page 792, issue of November 15.

JANUARY 8. New England Society of Anesthesiologists. Page 996, issue of December 20.

JANUARY 8. Springfield Academy of Medicine. Notice above.

JANUARY 8–31. Boston City Hospital House Officers' Association. Page 1032, issue of December 27.

JANUARY 9. Essex North District Medical Society. Page 996, issue of December 20.

JANUARY 10. Tufts Medical Alumni Lecture. Page 996, issue of December 20.

JANUARY 10. The Recognition and Management of Common Kidney Diseases. Dr. Robert P. McCombs. Pentucket Association of Physicians, 8:30 p.m. Haverhill.

JANUARY 14–19. School of Cytology. Page 956, issue of December 13.

JANUARY 15. Harvard Medical Society. Notice above.

JANUARY 16. Greater Boston Medical Society. Notice above.

JANUARY 17. Boston Gastroenterological Society. Page 996, issue of December 20.

JANUARY 22, FEBRUARY 26, MARCH 25 AND APRIL 24. Norfolk District Medical Society. Page 710, issue of November 1.

JANUARY 23. New England Conference on Allergy and Related Subjects. Page 996, issue of December 20.

JANUARY 23. Suffolk District Medical Society. Page 669, issue of October 25.

MARCH 10–13. New Orleans Graduate Medical Assembly. Page 956, issue of December 13.

MARCH 12. Northeastern New York Radiological Society. University Club, Albany, New York.

MARCH 31–APRIL 4. Fifth American Congress on Obstetrics and Gynecology. Page 832, issue of November 22.

MAY 1–3. American Goiter Association. St. Louis, Missouri.

JULY. Commonwealth and Empire Health and Tuberculosis Conference. Page 792, issue of November 15.

JULY 7–12. International Diabetes Federation. Page 996, issue of December 20.

(Notices concluded on page xv)